Acute Behavioural Tolerance to the Effect of Alcohol on Information Processing, Response Inhibition, and Subjective Intoxication

Ross Edward Comley

Bachelor of Psychology (Hons)

School of Psychology

University of Adelaide

A Thesis Submitted in

Fulfilment of the Requirement of the Degree of

Doctor of Philosophy (PhD)

2020

Abstract

Acute tolerance is a rapid decrease in the effect of alcohol relative to the size of the dose. This thesis is comprised of four manuscripts (Comley & Dry, 2020a; Comley & Dry, 2020b; Comley & Dry, under review-a; Comley & Dry, under review-b), each addresses a limitation in our understanding of the effect. The aims of the literature review (Comley & Dry, 2020a) were to examine paradigms for observing acute tolerance, identify what evidence has been found, identify domains of behaviour where it occurs, and ascertain which conditions influence it. Seven different research paradigms were identified. The effect was found to be prevalent, but not uniform across different behavioural measures. The evident uncertainty around which measures are susceptible to acute tolerance prompted the undertaking of two experimental studies. The first study (Comley & Dry, 2020b) examined acute tolerance in subjective intoxication, and in two cognitive domains: information processing speed measured using the Inspection Time Task, and response inhibition measured using the Sustained Attention to Response Task. An acute tolerance effect was found in ratings of subjective intoxication and Inspection Time Task performance. The second study (Comley & Dry, under review-a) investigated acute tolerance in subjective intoxication, response inhibition measured using the Stop-Signal Paradigm, and executive and psychomotor speed measured using a Multiple-Choice Reaction Time task. This paper also examined the influence of dose-size on acute tolerance. An acute tolerance effect was only seen in ratings of subjective intoxication, and only under the higher dose. The fourth paper (Comley & Dry, under review-b) reports an additional examination of the ratings of subjective intoxication from the second study. Acute tolerance to subjective intoxication was examined using three different paradigms identified in the literature review. In all three paradigms, an acute tolerance effect was observed in the high dose condition, but not in the low dose condition.

Statement of original authorship

I declare that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. In addition, I declare that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that the copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also permit the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for any period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

List of Publications by Candidate

Published Journal Papers

Comley, R. E., & Dry, M. J. (2020). Acute behavioural tolerance to alcohol. *Experimental and Clinical Psychopharmacology*, *28*(1), 112.

Comley, R. E., & Dry, M. J. (2020). Acute tolerance to alcohol-induced impairment in cognitive performance. *Experimental and Clinical Psychopharmacology*.

Manuscripts submitted for publication

Comley, R. E., & Dry, M. J. (Under Review). Acute tolerance to subjective intoxication from alcohol.

Comley, R. E., & Dry, M. J. (Submitted for publication). Acute tolerance to alcohol in objective and subjective measures.

Acknowledgments

In acknowledging those people who made this possible, priority goes to my supervisors Dr Matthew Dry and Professor Nicholas Burns. I wish to express my gratitude to Dr Dry for his willingness and open-mindedness to supervise my candidature, and for providing the guidance that enabled me to complete this thesis. I also wish to thank Prof. Burns for the time that he provided and his expertise that was so generously given throughout this project.

Programming support for this project was provided by Dr Irina Baetu, Nathan Beu and Lauren Kennedy. Maureen Bell provided assistance with the literature search for the review.

Of course, I must also acknowledge the support of my family and friends through this journey, they made it less difficult than it needed to be.

Finally, Skye. Thank you for being so very patient.

Table of Contents

List of Figures

List of Tables

A note on fonts used in the thesis

Two fonts have been used to provide some means to of discerning the content of this thesis from the published/submitted material included in it.

The thesis appears in Times New Roman.

The manuscripts for publications appear in Georgia.

Chapter 1: Introduction

Alcohol, its Effects on Behaviour, and Acute Tolerance

This thesis is on the topic of alcohol, specifically acute tolerance to the effects of alcohol on behaviour. Acute tolerance is a rapid decrease in the strength of the effects that alcohol causes. A review of previous studies on acute tolerance is presented in Chapter 2 (Comley & Dry, 2020-a). In the review, we identified a gap in the understanding of which cognitive domains are susceptible to acute tolerance, which prompted the undertaking of two experimental studies. The findings are reported in Chapter 3. The first study (Comley & Dry, 2020-b) examined acute tolerance in subjective intoxication, information processing, and response inhibition. The second study (Comley & Dry, under review-a) investigated acute tolerance in subjective intoxication, response inhibition, and executive and psychomotor speed. This paper also examined the effect using two different dose sizes. The fourth paper (Comley & Dry, under review-b) reports an additional examination of the subjective intoxication measure from the second study.

As this thesis concerns alcohol, some introduction to what the substance is and what it does is needed. Alcohol doesn't abide by typical pharmacological nomenclature because the substance and names for it were widespread well before such standards became convention. In a technical sense, an "alcohol" is any organic compound with a hydroxyl (OH) functional group attached to a carbon atom (McNaught & McNaught, 1997). This definition includes a broad range of chemical compounds but derives from the word for the active ingredient common to fermented and distilled beverages, which is specifically ethyl alcohol (EtOH), or *ethanol*. Ethanol is a simple alcohol made up of the –OH functional group attached to an alkyl group with two carbon atoms (Figure 1) (National Centre for Biotechnology Information, 2020). As *alcohol* is the word most commonly used to refer to alcoholic beverages and their active ingredient (ethanol), this will be the case for this thesis.

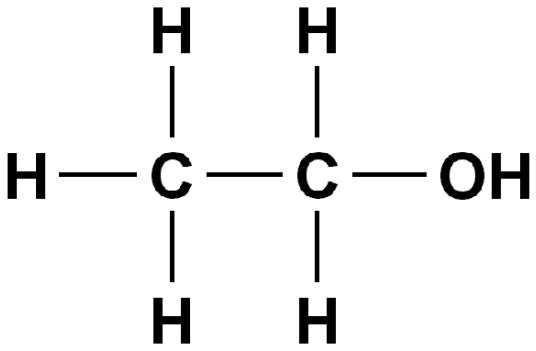


Figure 1: An Ethanol molecule, C-2H-5OH

Alcohol is arguably mankind's most popular and most harmful drug (Edward, 2013). Its popularity and its capacity for harm are two predominant reasons for researching the effects that alcohol has on behaviour. It is a unique 'substance'. Mankind has been consistently drinking it for thousands of years, and its psychoactive effects have become a commonly known and essential characteristic. Consumption causes an array of acute effects and produces an altered state of consciousness called intoxication or drunkenness (Fox & MacAvoy, 2010). Intoxication is associated with an array of different physiological and psycho-social harms (Healey, 2011); despite which, alcohol has always been remarkably popular. Mankind has had a long, close history with alcohol that has evolved into a trillion-dollar per year[1] feature of modern culture which we can expect to last (Statista, 2020).

1.1 A Brief History of Alcohol

In comparison to other types of alcohol, ethanol has had a much closer relationship with life on earth. This is because ethanol is the primary product of fermentation by certain types of yeast; a microscopic, single-celled fungus that evolved on earth two billion years ago (Kurtzman & Fell, 2006). Yeast produce ethanol from sugar through fermentation [$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO$] which affords the yeast an advantage over competitor species that can't metabolize or tolerate ethanol[2] (Hagman, Säll, Compagno, & Piskur, 2013; Dashko, Zhou, Compagno, & Piškur, 2014). As wild

[1] This can be compared with an $800 million cigarette market, and 165 billion dollar cocaine market (USD)
[2] Yeast sacrifice ATP from aerobic metabolism to produce alcohol, starving out and poisoning competitors.

yeast occupy an array of habitats and temperate zones and are pervasive in the air wherever plants grow, alcohol produced by wild yeast is found widely in nature (Hart, Ksir, & Ray, 2013). Consequently, alcohol has been an available food source for life on earth since well before the existence of mankind. Overripe fruit is a common source, the sugar-rich juice provides perfect water and nutrition for yeast to thrive (McGovern, 2009).

Due to the pervasiveness of yeast, fermentation of sugars often takes place in the gut, and many forms of complex life evolved mechanisms for alcohol metabolism that allowed for its inclusion in the diets of various insects and animals (Danielsson & Jörnvall, 1992). Most animal species do not possess a natural interest in consuming alcohol, but there are still many species which do, and even some which will deliberately seek it out, including elephants, birds and the pen-tailed tree shrew (Wiens et al., 2008; Zielinski, 2011). Alcohol seeking behaviour is also observed in many primate species (Dudley, 2004). Chimps, monkeys, gorillas and baboons are seen to seek out fermented fruits in preference to ripe ones at certain times, especially in warm tropical climates where fermentation can occur on the bush or tree. Early hominids had smaller teeth well adapted for eating foods like fruits and would have shared this preference for energy-rich, fermented fruit as an adaptive strategy in a resource-scarce environment (Dudley, 2000). Consumption of alcohol is therefore, a pre-human behaviour that predates our speciation. It is impossible to determine exactly when and where the first human consumption of alcohol occurred because there would have been repeated instances throughout the evolution of hominids into humans. Alcohol is unique as a substance because its use was not adopted or invented, it was inherited.

Fermented foods have remained in our diet ever since they were a small part of the diet of proto-humans (Dudley, 2000). Because fermentation occurs naturally and is often hard to avoid, discovering methods of production were likely accidental (Hames, 2014). Repeated experiences of Palaeolithic containers filled with fruit becoming contaminated with yeast and producing something akin to Stone Age wine likely occurred many times in different places; and at some point in humanity's very early pre-history we used our limited knowledge of natural fermentation to

deliberately produce alcohol (Hames, 2014). Since then, the popularity of alcohol has demanded a significant amount of mankind's attention and resources be dedicated to its production

Fermenting produce has been a near universal human practice. Alcoholic fermented beverages can be divided into beer, made from grains and cereals; and wine, made from sap, honey, milk and fruits (most often grapes). The earliest archaeological evidence of alcohol production comes from Israel, where a gruel-like beer was being brewed as early as 13,000 years ago (Liu et al., 2018). For most of human history the primary reason to produce alcohol was for preservation (Hanson, 2013). Parasites and microbes which spoiled local water supplies could be killed off through the process of producing alcohol (Unger, 2004; Dasgupta, 2011). But there are also nutritional advantages to fermenting produce (McGovern, 2009).

A monumental change in the production, consumption and trade of alcohol was brought about by the discovery of distilling fermented alcohol into stronger 'spirits' in the 10th century[3]. The discovery of distillation was a pharmacological revolution, creating the world's first 'synthetic' drug (McKenna, 1999) and allowing the production of a beverage with an alcohol content greater than 15% for the first time (Hart et al., 2013). Public drunkenness only became a punishable offence in many parts of Europe after the distilling revolution. Alcohol's relationship with mankind was also transformed by industrialization making mass production possible (Smith, 2008). As working conditions changed with industrialization, drinking became something done specifically outside of work rather than throughout the day. The increased production lead to increased consumption, which then lead to increased abuse and greater efforts at regulation. However, such efforts were often futile (Hames, 2014). In 18th century Britain, the strict regulation on gin was met with riots. Similarly, US prohibition laws introduced in the early 20th century were quickly repealed when they were seen to increase organized crime (Phillips, 2014).

[3] Distillation is a process by which the vapours from a heated solution of alcohol are collected and condensed into a liquid again, producing distillates with higher alcohol percentages than the initial ingredients

1.2 The Current Situation

Despite our long history with alcohol, its consumption is still associated with an array of negative consequences that suggest we have not entirely mastered its use (Winstock, Barratt, Maier, & Ferris, 2018). Currently, billions of dollars are spent every year consuming alcohol, regulating its use, and repairing the damage it causes (Vaccarino, 2004). Billions of people drink alcohol, and millions of them have consumption patterns that could be called "unsafe" (Hart et al., 2013). In pre-modern conditions alcohol mainly served nutritional as well as pharmacological purposes in societies. But, with increasing access to food and water as well as advancement in production methods, people have gradually shifted the place of alcohol in society to more specifically serve pharmacological aims (Müller & Schumann, 2011). Given that the behavioural effects of alcohol are associated with a range of harms, its popularity as a substance appears to be an ever-growing concern (Hingson & White, 2013; Patrick, 2016).

The negative effects of alcohol on health have long been known to man, but this has done little to curb our consumption. Worldwide, an estimated one in three people, or 2.4 billion, consume alcohol in some quantity regularly (WHO, 2019). In 2018, global sales of alcohol exceeded $1,000,000,000,000 US, and market forecasts do not expect this figure to decrease (ISWR, 2019). The global per capita consumption rate is approximately 6.2 litres of pure alcohol per person per year, or the equivalent of one litre of wine per week (WHO, 2019). However, consumption rates vary between countries. The highest consumers are developed countries[4], while the lowest consumers are found in South East Asia and the eastern Mediterranean. Genders also differ in consumption patterns, with average daily consumption rates being approximately 0.7 drinks for women and 1.7 drinks for men (WHO, 2019). Despite the widespread popularity of alcohol most of the world's population does not drink frequently. Records from 2014 suggested that 61.7% of adults had not drunk any alcohol at all in the previous twelve months, while 48% had never drunk it in their lives. This demonstrates how the per capita consumption mentioned above does not perfectly reflect the consumption patterns of actual

[4] The top 5 (litres of pure alcohol per capita/year, age 15+) being the Czech Republic (14.1L), Australia (12.5L), Portugal and Slovakia (both 12.5L), and Hungary (12.4L).

consumers. In reality, only a minority of those people who do drink are responsible for a large majority of consumption, and a significant portion of alcohol is consumed in episodes of heavy drinking[5], where greater levels of intoxication are reached (Ritchie & Roser, 2019).

Except for tobacco, alcohol accounts for a higher burden of disease than all other drugs. Each year, 3.3 million deaths are the result of alcohol consumption and about a quarter of these are from injuries (WHO, 2019). The Australian drug harm ranking study ranked alcohol above tobacco, methamphetamine and cannabis as the most harmful substance overall (Bonomo et al., 2019). One of the most obvious harms arising from alcohol consumption is the development of addictive patterns of use. Alcohol use disorders are more prevalent than other substance use disorders, and Alcoholism ranks first for lifetime prevalence rate for all psychiatric disorders[6] (Leonard, 2003).

The impairment to reasoning, motor-skills, cognitive ability and perception characteristic of intoxication causes an array of harms. Alcohol is responsible for 17.1% of deaths by accidental injuries including 16% of deaths from falls and 15% of deaths from traffic injuries (WHO, 2019). Research also suggests that people assess risk less accurately when intoxicated, which increases the likelihood of engaging in risky activity (Graham, 2008). One of the major causes of death in people aged 15-29 in Europe is driving under the influence of alcohol (Mitis & Sethi, 2012). 'Drink Driving' is still a major public safety issue despite both widespread knowledge of the impairment to driving that intoxication causes, and the illegality of driving with an elevated blood alcohol content in many countries.

In its 2014 report on the global status of alcohol, the World Health Organisation stated that crime and violence are probably the most significant social problems created by the harmful use of alcohol (WHO, 2014). An estimated 63% of all violent crimes worldwide involve the use of alcohol. Although most people who drink will not become aggressive, there is a positive correlation between violent crime and alcohol use, and greater intoxication is related to greater severity of aggression

[5] Defined as consuming at least 60 grams of pure alcohol on a single occasion
[6] Estimates of worldwide cases of Alcohol Use Disorder (AUD) from 2016 were 100.4 million, compared with opioid dependence (26.8 million cases) and cannabis (22.1 million cases) (Connor, Haber, & Hall, 2016)

(Graham, 2008). Heavier drinking is seen to be associated with more frequent engagement in domestic violence, with binge drinking generally being associated with the most regular and serious manners of aggression (Kahler, McCrady, & Epstein, 2003). Alcohol abuse also increases the risk of both experiencing and perpetrating sexual violence, and due to its availability and legality, the majority of sexual assaults involve alcohol. Although alcohol is neither a necessary or sufficient cause of aggressive behaviour a meta-analysis of experimental research by Bushman (1997) suggests at least a partially causal link.

1.3 The Effect of Alcohol on Behaviour

The effects of alcohol on behaviour have not been ignored by researchers. Alcohol was in fact one of the earliest interests of psychology. A review of experimental studies on the behavioural effects of alcohol by Jellinek and McFarland (1940) refers to studies from as early as 1851. Because of this long history, we already have a respectable understanding of what intoxication is and how alcohol causes it.

Before alcohol can begin to have effects on behaviour, it must first reach active sites in the brain. Like any drug, alcohol requires a route of administration, and oral consumption performs this function perfectly well, being easily absorbed from the gastrointestinal tract after being swallowed (Agarwal & Goedde, 2012). Although there are alternative routes of administration, these are so uncommon that our discussion can be limited to oral consumption as the standard practice (Vaccarino, 2004). When drunk, most of the dose (≈ 85%) is absorbed in the small intestine where the large concentration of blood vessels provides easy access to the arterial bloodstream. From the bloodstream alcohol can make contact with the cells of virtually all organs (Kuhn, 1998). The hydrophilic qualities of Ethanol molecules cause it to accumulate in tissues with higher water content[7] (Meyer & Quenzer, 2005). The rate that alcohol is absorbed into the bloodstream, brain and organs, is influenced by several factors, such as; the concentration and size of the dose, blood flow, contents of the stomach, nutrient deficiency, temperature, physical activity (Dasgupta, 2011). Aside from these factors, a high

[7] A dose of equivalent size tends to produce higher blood alcohol concentrations in females, due to females having less total body water % than males, on average.

degree of individual variation in ethanol absorption has been documented (Wagner, 1972). Carbonated drinks can also accelerate the movement of alcohol from the stomach into the intestine, increasing the rate of absorption (Roberts & Robinson, 2007). All of these factors can contribute to the inter-individual variability of blood alcohol concentration (BAC) following the ingestion of a fixed amount.

Ninety-five per cent of alcohol absorbed into the circulatory system is metabolized in the liver and removed as carbon dioxide via the blood and lungs, and water via urine. The remaining five per cent is excreted by the lungs, allowing for the measurement of BAC from its concentration in a sample of breath (Kuhn, 1998). The primary enzymes in the liver that break down alcohol are *alcohol dehydrogenase* (ADH) which converts ethanol to acetaldehyde, and *aldehyde dehydrogenase* (ALDH) which converts the acetaldehyde into acetic acid that is then further oxidised to produce carbon dioxide and water[8]. The major determinant of the rate of alcohol metabolism is ADH activity (Dasgupta, 2011). Although several "home-remedy" suggestions for accelerating alcohol elimination exist, such as exercise or coffee, none of these things affects the activity of the enzyme. Some ADH is present in the stomach, causing first-pass metabolism; wherein some of the dose is metabolised before reaching the bloodstream (Carrigan, 2019). The rate which alcohol is oxidized remains constant over time regardless of its concentration in the blood. However, the rate of metabolism is substantially variable person-to-person, averaging 12-18 ml of pure alcohol per hour (Agarwal & Goedde, 2012). As the metabolic rate is constant, alcohol can accumulate in the blood when consumption is faster than metabolism. For example, a person who can metabolise 15ml of alcohol per hour, drinking three standard drinks (10ml of pure alcohol) per hour, will accumulate 15ml of alcohol in the blood per hour.

The relatively simple nature of the ethanol molecule means it can easily cross membranes like the blood-brain barrier. Like all drugs, the effects of alcohol result from its chemical structure and shape, which allows it to interact with receptors and neurotransmitters in the brain (Meyer & Quenzer,

[8] One reason why co-ingestion of alcohol with other substances can be potentially dangerous is because the enzymes in the liver become competed for by the two substances.

2005). There is no specific alcohol receptor. Rather, alcohol affects a range of endogenous chemicals by altering the configuration of their binding sites, generally depressing synaptic activity and making its neurochemical actions resemble those of other sedative drugs (Kuhn, 1998). Most neurotransmitters and receptors appear to be altered in their functioning to some degree by alcohol, but the primary neurotransmitters affected by alcohol are glutamate, GABA[9], dopamine, adenosine, serotonin and opioid peptides (Leonard, 2003).

Alcohol blocks the effects of glutamate, a major excitatory neurotransmitter (Bear, Connors, & Paradiso, 2007). At BAC's as low as 0.03% alcohol inhibits glutamate from binding to the NMDA[10] receptor on neurons, decreasing excitatory signalling in the brain (Meyer & Quenzer, 2005). This altered signalling also reduces the release of other neurotransmitters such as norepinephrine and acetylcholine. As glutamate action at NMDA receptors contributes to associative learning, alcohol is often seen to impair learning and memory function (Kuhn, 1998). GABA on the other hand is the brains primary inhibitory neurotransmitter. Alcohol increases the inhibition produced by GABA, resulting in anti-anxiolytic and sedative effects. Alcohol also increases the overall concentration of GABA by inhibiting its degradation. Nearly all drugs which stimulate GABA activity have anxiolytic effects, and this reduction in anxiety partly explains the widespread social use of alcohol and the association between alcohol abuse and anxiety disorders (Bear et al., 2007).

Alcohol also gives a sense of euphoria by increasing dopamine activity in the nucleus acumbens, an area of the brain associated with behavioural reinforcement and addiction (Vaccarino, 2004). Dopamine itself does not excite or inhibit neurons but alters their sensitivity to other neurotransmitters, especially glutamate (Fox & MacAvoy, 2010). Further reinforcement is provided by an increase in endogenous opioid synthesis and release. Opioid peptide neurotransmitters such as endorphins and enkephalin promote analgesia and modulate pain. The release of serotonin, which plays a role in the regulation of behaviour, emotions and mood, as well as arousal, sleep, appetite and consumption behaviours is increased by alcohol (Bear et al., 2007). Alcohol also affects the

[9] γ-aminobutyric acid
[10] *N*-methyl-D-aspartate

interaction of serotonin with other neurotransmitters like GABA and dopamine. For example, in the presence of alcohol, serotonin in the hippocampus contributes to memory loss and impaired judgement (Fox & MacAvoy, 2010).

The resultant combination of the increased function of inhibitory neurotransmitters and the diminished function of excitatory ones produces an overall depressant effect on the central nervous system. This causes activity in the central nervous system to slow down, resulting in the increased time needed for reactions to stimuli, impaired decision making and impaired motor control (Meyer & Quenzer, 2005). Although alcohol is often referred to as having stimulant qualities, these are largely explained by the depressive effects, as the inhibitory centres of the brain which modulate behaviour also have lower excitability under alcohol (Fox & MacAvoy, 2010). In addition, the stimulant effects are also attributable to the increase in dopamine activity caused by alcohol.

These neuro-chemical effects produce a variety of short-term changes in a person's behaviour. According to the American Psychological Association intoxication is defined as "a reversible condition that develops soon after the ingestion of alcohol. It comprises behavioural or psychological changes, such as inappropriate or aggressive behaviour, impaired judgment, or impaired social functioning; and physiological changes, such as slurred speech, unsteady gait, and disruption of attention or memory (VandenBos, 2007). The effects typically become more noticeable with increased alcohol intake. When examining the acute effects of alcohol, it is not appropriate to measure the dose-size by the total weight or volume of alcohol administered because the amount of alcohol acting on the brain will vary through the duration of the dose as it is absorbed, distributed and metabolized. The BAC provides a contemporaneous measure of dose that reflects the amount of alcohol acting on the brain at the time measures of the effect of alcohol are taken.

The extent of alcohol's distribution in brain regions correlates with its concentration in the blood[11] (i.e. brain alcohol concentration approximates BAC; Dasgupta, 2011). The effects of alcohol

[11] Because the size of a dose of alcohol does not correlate with the volume of the drug able to be active at a particular time after ingestion, the BAC is used as a contemporaneous measure of dose-size.

on behaviour are seen to change and increase with increasing BAC as more of the drug starts acting on the active sites in the brain (see Table 1). During the initial stages after consumption, feelings of pleasure and relaxation occur and people usually become more talkative and socially outgoing. These early phases then give way to feelings of sedation leading to a more quietened state and withdrawal (Kuhn, 1998). The depression of the central nervous system produces subjective feelings of merriment, loquacity, reduces inhibition, increases risk-taking behaviour and impairs judgement.

Complex, abstract, and poorly learned behaviours are most vulnerable to impairment from alcohol and are disrupted at the lowest effective BACs. At BAC's below .05%, alertness and inhibition are lowered leading to some impairment in judgement. With increasing doses, simpler behaviours and gross motor performance are also seen to deteriorate (Dasgupta, 2011). At 0.1% reaction times are noticeably slower and motor function becomes noticeably impaired. With further increases past 0.15%, impairment in reaction time becomes consistently greater. At 0.2% there is marked depression in sensory and motor capability, and at 0.25% motor skills are severely disturbed causing noticeable staggering and ataxia. At higher doses past 0.3%, people have a complete lack of comprehension of their current environment and suffer severely impaired coordination, unsteady gait, involuntary eye movement (nystagmus), memory deficiency, inattention, and stupor (Meyer & Quenzer, 2005). A commonly reported experience after drinking is a failure to recall events during the drinking session. In cases of very high consumption entire segments of time are completely forgotten, but alcohol can impair the ability to form new memories even at relatively small doses. In extreme cases of intoxication, people will fall into comas and vital areas of the brain shut down leading to respiratory failure. LD1 is reached at a BAC of 0.35% and LD50 at 0.4%[12] (Hart et al., 2013).

Cognitive processes are typically affected at a lower BAC than psychomotor abilities. Cognitive processes are basic mental abilities, while psychomotor abilities are those functions involving muscular activity resulting from mental processes. Observable impairment usually only occurs at BACs above 0.03%. However, effects have been seen at lower levels (Dasgupta, 2011). The predominant factor in determining the magnitude of the effect of alcohol is the size of the dose or the

[12] The size of a lethal dose (LD) for 1% and 50% of the population

BAC. Another factor is the rate at which the BAC rises; the more rapid the increase, the stronger the effects. The effects at a given BAC are also influenced by the person's age, experience and the environment.

The study of the behavioural effects of alcohol is complicated by the influence of placebo effects. The expectations associated with consuming alcohol are pervasive in society, especially given the long history we have with alcohol: and we develop such expectations well before we even try alcohol for the first time (Hart et al., 2013). Thus, to be certain that the behavioural changes observed in an experiment are attributable to alcohol a balanced placebo design needs to be adopted, wherein approximately half of participants are given an active dose and the remainder are given a sham dose. Placebo doses are reliably shown to produce changes in behaviour that can be measured and compared with effects under an active dose to control for expectation effects. Placebo designs can also be used to control for practice effects that may occur when taking repeated measures from the same subject.

Table 1.
Blood Alcohol Concentration and behavioural effects.

BAC %	State	Behavioural Effects
0.40	Death	Brain areas that control involuntary actions like breathing and gagging become impaired
0.35	Coma	Loss of consciousness
0.30	Black Outs	Memory loss
0.25	Stupor	Loss of awareness of surroundings
0.20	Staggering	Severe feelings of illness
0.15	Severely impaired	Nausea and Vomiting Marked reduction in sensory and motor capacity
0.125		Exaggerated and intense emotions Slowed Reaction Time
0.10	Obvious impairment	Slurred speech Loss of balance, coordination
0.075		Mildly impaired judgement, less caution Decrease in reasoning and psychomotor skills
0.05	Mild Euphoria	Mood elevation
0.025	Slight Relaxation	Possible impairment of signal detection, visual detection, attention and hand eye performance
0.00	Sober	

1.4 Acute Tolerance

The *dose-effect* (dose-response) of a drug is the magnitude of the drug-effect produced from a dose of a given size. For example, 0.5 grams of alcohol per kilo of body weight (0.5g/kg) may produce a 10% impairment in performance on a psychomotor task. The *dose-response relationship* describes how the dose-effect changes with increases or decreases in the size of the dose (Hart et al., 2013; UN, 1997). As seen in the previous section, the dose-response relationship for alcohol is generally linear and positive (Pohorecky & Brick, 1990). Increases in the BAC cause an increase in the magnitude of effects. For example, visual information processing speed and working memory have been found to become more impaired as BAC increases (Dry, Burns, Nettelbeck, Farquharson, & White, 2012).

A linear dose-response relationship is not a pharmacological quality unique to alcohol. But in the case of alcohol, it has had a range of far-reaching implications. It has allowed for legally enforced limits on BACs during certain activities such as driving. In Australia, the legal limit for driving is a BAC of .05%, as this has been deemed to reduce alcohol-related road accidents and fatalities that are more likely under higher BAC's (South & Hawthorn, 1990). The linear dose-response has also allowed for the prescription of safe or responsible drinking practices. Less frequent, smaller doses that produce lower BAC's are less likely to produce negative outcomes in comparison to higher doses consumed more often (Brussen, 2010). The WHO suggests there is no safe level for drinking alcohol and advises that less is better (WHO, 2014). In comparison, 'Drinkwise Australia' an independent not-for-profit organisation established by the alcohol industry advises that drinking no more than two standard drinks on any day reduces the lifetime risk of harm from alcohol (DrinkwiseAustralia, 2019). In criminal courts, judges often comment on the amount of alcohol consumed when discussing influences for an offence and consider an offenders level of intoxication in sentencing (Cook, Creyke, Geddes, & Hamer, 2009). A simple and obvious consequence of alcohol's linear dose-response is that people who want to experience stronger effects of alcohol are going to drink more of it. People consuming alcohol to facilitate socializing, for coping with stress, for its anxiolytic effects, or the sake

of binge drinking will often ignore and/or exceed the recommended guidelines which only prescribe small doses incapable of producing the desired effects (Müller & Schumann, 2011).

Although the dose-response of alcohol is generally linear, variations within individuals are often observed (Fillmore & Vogel-Sprott, 1998). Changes in the dose-effect result in BAC's producing different magnitudes of effect for a given individual at different times. Accordingly, equivalent magnitudes of effect can be observed at different BAC's. These variations in the dose-effect are called sensitization and tolerance. Sensitization is an increase in dose-effect (Stewart & Badiani, 1993). When sensitization to a drug occurs, a dose of a given size will produce a greater magnitude of effect than on prior occasions. In contrast, tolerance is a decrease in the dose-effect, indicated by either a decreased magnitude of effect relative to the size of the dose or an increase in the dose size being needed to produce a previous magnitude of effect.

Tolerance can be classified in numerous ways. One manner of classification is by the level of biological complexity the effect is observed at. Aside from behavioural tolerance, which this thesis focuses on, tolerance can also occur at the molecular, cellular, and metabolic level (Pietrzykowski & Treistman, 2008; Wilson, Erwin, & McClearn, 1984). A decrease in dose-effect can also be classified by the time frame in which it is observed (Kalant, 1996). The type of tolerance people are more familiar with is *chronic tolerance*. Chronic tolerance is caused by the repeated exposure to alcohol over accumulative doses and is therefore observed between doses on separate occasions over an extended period of time (weeks/months/years; Martin & Moss, 1993; Bennett, Cherek, & Spiga, 1993). When chronic tolerance occurs, the magnitude of the effect produced by later doses is less than that produced by earlier doses of equivalent size (Figure 2). For example, a person who regularly consume an entire bottle of wine every night would eventually find the strength of the effects produced by a dose of that size (i.e., one bottle) were not as strong as they once were. Chronic tolerance is seen to increase with total consumption and is higher in people with alcohol use disorder (Hoffman & Tabakoff, 1996).

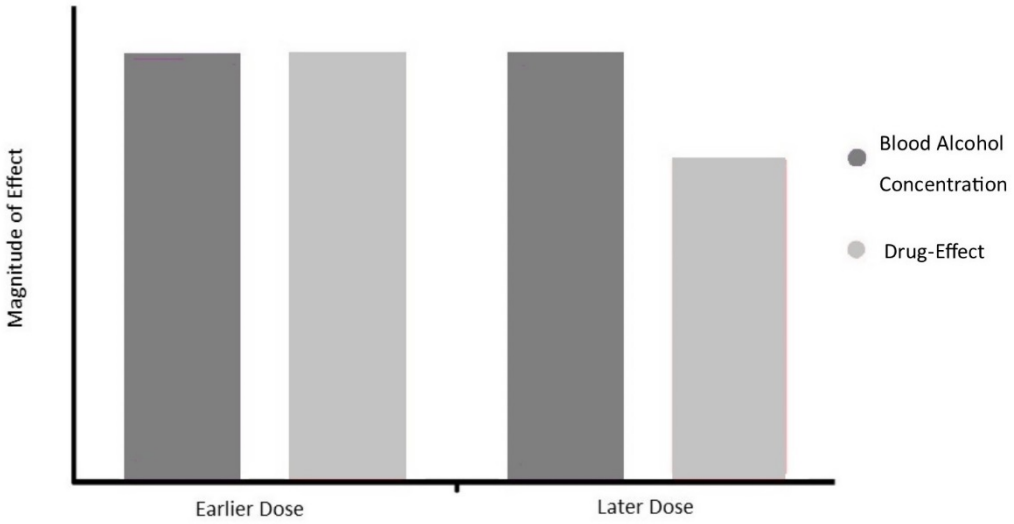


Figure 2. BAC vs Dose-effect between earlier and later doses showing Chronic Tolerance

A less well-known form of tolerance, which occurs on a much smaller time scale, is called *acute tolerance*. In contrast to chronic tolerance, wherein a decrease in the dose-effect is observed *between* doses, acute tolerance occurs virtually immediately after alcohol is administered, and is thus seen *within* the duration of a single dose of alcohol (Tabakoff, Melchior, & Hoffman, 1982). Because acute tolerance occurs within the time a single dose of alcohol is eliminated, a change in the dose-effect cannot be observed by comparing the magnitude of effect between doses. Instead, acute tolerance is examined by treating the BAC as a contemporaneous measure of dose-size and examining changes in the strength of the drug-effect relative to the BAC, across different time-points during the dose (Rigter & Crabbe, 1980). When acute tolerance to alcohol occurs, the dose-effect, relative to the BAC, is greater at the earlier stages of a dose, and smaller in later stages of its duration.

The first record of acute tolerance being empirically demonstrated was by Sir Edward Mellanby in 1919 (Ginsburg, Martinez, Friesenhahn, Javors, & Lamb, 2008). In his study, Mellanby details a rudimentary experiment in which he gave a dose of alcohol to four dogs (and one man) and observed the pattern of drug-effect over the dose's duration (Mellanby, 1919). The change in BAC produced by a single dose of alcohol follows a reliable curve. After administering a dose of alcohol in a single bolus serve, BAC initially rises "quickly" from baseline-to-peak, and then declines less quickly back to baseline (Watson, Watson, & Batt, 1981). Mellanby reported that the dogs displayed more impairment in their balance and coordination (Ataxia) at a given BAC earlier in the dose when

the BAC was rising to its peak, than at later times in the dose when BAC was decreasing (Mozayani & Raymon, 2003). Mellanby did not refer to this pattern of impairment as "acute tolerance" in his study, but his experimental design which compared the magnitude of drug-effect between equal BAC's on each limb of the BAC curve became repeatedly used to show a decrease in the dose-effect of alcohol. Hence, acute tolerance observed between the ascending and descending limbs of the BAC curve is commonly referred to as the "Mellanby effect". It was initially argued that the reduction in effect was merely the result of practice effects, with improvement on the descending limb developing from the administration of measures on the ascending limb. However, many subsequent investigations demonstrating the phenomenon occurring independently of such confounds gradually emerged in the literature, especially in animal studies, and several reviews on the topic confirming the existence of the effect have been published (Le & Mayer, 1996; Rigter & Crabbe, 1980).

Despite an established basis in the literature, the understanding of acute tolerance is actually very limited. While past reviews have provided strong support for the existence of the effect, even a cursory reading of the literature would find instances where the effect has not been found when expected. Also, like alcohol effects in general (Fogarty & Vogel-Sprott, 2002), acute tolerance shows variability between different behavioural measures and different dose sizes (Rigter & Crabbe, 1980; Vogel-Sprott, 1979). Because of this, it is somewhat unclear exactly how reliable acute tolerance is and when it can be expected to occur, if at all. The utility of improving our understanding of acute tolerance is obvious when the potential consequences of a rapid change in the dose-effect of alcohol during a real-world drinking session are considered. Public health and safety campaigns have often tried to reduce the harms of alcohol consumption by prescribing safe or responsible drinking practices (Edward, 2013). Awareness and understanding of how the dose-effect changes with acute tolerance has the potential to inform decisions regarding drinking practices, aid in the management of consumption patterns, and reduce the harms caused by alcohol.

This thesis aimed to investigate acute behavioural tolerance to alcohol and further our understanding of the effect. The manuscripts for four publications are presented in the following Chapters. The first manuscript is a literature review. The second, third and fourth manuscripts detail

two experimental studies examining acute tolerance in subjective intoxication, and several cognitive performance measures.

Chapter 2: A Review of the Literature

2.1 Explanatory Statement

Prior to this literature review, the available reviews on acute tolerance had at least one of two limitations. They either focused solely on studies using Mellanby's experimental design or they were not recent enough to provide a comprehensive overview of the current literature. Mellanby's method of comparing the dose-effect between the limbs of the BAC curve has not been the only method used to observe acute tolerance (Wilson & Nagoshi, 1987). Methods that allow for comparison of the drug-effect between multiple times in the time course of a dose of alcohol, while controlling for the changes in BAC that occur during the absorption and elimination of alcohol, can also provide a valid examination of changes in the dose-effect (Martin & Moss, 1993), and differences in experimental designs can allow for the limitations of particular designs to be overcome. Although recent reviews focusing on studies using Mellanby's paradigm have provided valuable insight into the Mellanby effect, the inclusion of multiple research designs is needed for a comprehensive synopsis of the topic of acute tolerance. The most recent review we found that included multiple paradigms was Le and Mayer (1996), after which a considerable number of studies have been published.

There have been two recent reviews on the topic of acute tolerance. Schweizer & Vogel-Sprott (2008) focused on studies examining acute tolerance in cognitive tasks that gauged performance with either speed or accuracy measures, or both. A relatively small sample of six studies using the Mellanby paradigm was reviewed and found a reliable difference in acute tolerance between speed and accuracy measures. The authors showed that measures of the speed of cognitive processing tend to find acute tolerance, but measures of accuracy tend not to show the effect.

Holland and Ferner (2017) more recently published a broader review on the topic that did not restrict the included studies to those which used specific measures. They reviewed 27 studies on acute tolerance, which included 26 different measures of performance. The focus of the review was on the evidence for the "Mellanby effect". Therefore studies were restricted to those comparing data from both limbs of the BAC curve.

The authors concluded that subjective feelings of intoxication show the Mellanby effect. But, they go on to add that "the effect is not seen when BAC is held constant" (Holland & Ferner, 2017). This conclusion is based on the findings from three studies, Kaplan, Sellers, Hamilton, Naranjo, and Dorian (1985), Hendershot et al. (2015), and Zoethout et al. (2009). Kaplan et al. (1985) did indeed report an absence of acute tolerance to subjective intoxication using their steady-state design (discussed in the following review). However, Hendershot et al. (2015) clearly state their "Results implied acute tolerance to stimulant effects…..during the BAC plateau". Zoethout et al. (2009) also reported an acute tolerance effect and state "VAS[13] alertness and VAS alcohol effects showed variations in effect over time, despite stable alcohol levels" (See Figure 3). Whether acute tolerance occurs under steady state conditions is important to consider, because if it is only seen when comparing between limbs of the BAC curve, then the effect may be dependent on whether the BAC is increasing or decreasing. Holland & Ferner (2017) also reported that objective measures generally showed "greater impairment" or sensitivity on the descending limb; which conflicts with Schweizer & Vogel-Sprott's (2008) conclusion that the speed of cognitive processes show acute tolerance.

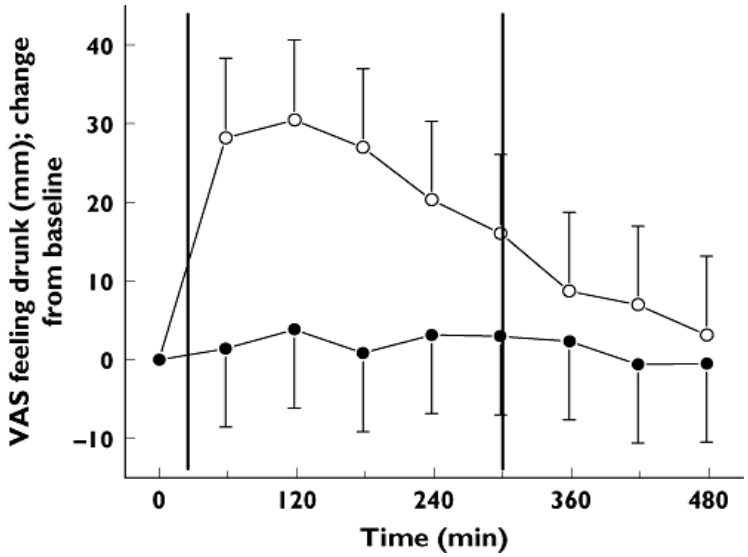


Figure 3: From Zoethout et al. (2009) "LS Means graph of visual analogue scale (VAS) alcohol effects (mm): change from baseline with 95% CI error bars. The plateau phase is marked by the two vertical lines. Ethanol (—○—); Placebo (—●—)"

[13] A subjective measure of alcohol

Because of these conflicting findings in the recent reviews, and the length of time since a review included paradigms other than Mellanby's; there was a place for an up-to-date, broader review of the literature on acute tolerance. To address this gap, the literature review for this thesis was undertaken with the intention of it being a published article. An additional aim of the literature review was to identify any areas in the literature that could be addressed within the scope of this thesis, and provide information on methods for researching the effect that could be adopted.

Statement of Authorship

Title of Paper	Acute behavioural tolerance to alcohol
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Comley, R. E., & Dry, M. J. (2020). Acute behavioural tolerance to alcohol. *Experimental and Clinical Psychopharmacology*, *28*(1), 112.

Principal Author

Name of Principal Author (Candidate)	Ross Edward Comley		
Contribution to the Paper	Literature search, drafting manuscript		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19/10/2020

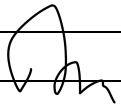
Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Matthew Dry		
Contribution to the Paper	General guidance as supervisor		
Signature		Date	20-10-20

2.2 Manuscript: Acute Behavioural Tolerance to Alcohol

Acute Behavioural Tolerance to Alcohol

R. Edward Comley

Matthew J. Dry

Abstract

Although the strength of the effect produced by alcohol is generally dose dependent, its effect on behavior cannot be reliably predicted by the dose alone because the dose effect has been shown to vary. Acute behavioral tolerance is a rapid decrease in the dose effect of alcohol, seen to occur within the duration of a single dose. Numerous research paradigms have been used to examine acute behavioural tolerance, across an array of different behavioral measures. We have reviewed studies that used a research paradigm appropriate to test for acute behavioral tolerance. The primary aim was to examine the different paradigms that have been used to identify what empirical evidence of the effect has been found. The additional aims were to identify domains of behavior in which acute tolerance has been shown to occur and ascertain which conditions have been shown to influence it. Findings of acute tolerance were prevalent. Seven different research paradigms were identified, and each found evidence of acute behavioral tolerance in at least one study. The effect was not uniform across all behavioral measures. Subjective measures reliably showed the effect, but objective measures of behavior were less reliable, providing evidence that particular aspects of task performance are more sensitive to acute tolerance than others. The dose effect of alcohol for behavioral measures is often shown to decrease within the duration of a single dose. Investigations into, and considerations of, the effects of alcohol on behavior need to consider temporal changes in the dose effect.

Keywords: alcohol; acute tolerance; Mellanby effect; BAC-time curve; dose–response relationship

Public Health Significance Statement

The effect of alcohol on behavioural measures has often been found to decrease within the duration of a dose. This decrease is not universal, and was seen to vary between different behavioural measures. Subjective measures more reliably show acute tolerance than objective measures, and this difference between behavioural domains raises concerns regarding issues like binge drinking and drink driving. Guidance for responsible drinking and future research into the effects of alcohol should consider the demonstrated decrease in the effect of alcohol, and the variability in the dose-effect between different domains of behaviour**.**

Introduction

Alcohol (as ethanol) is arguably our species most popular psychoactive drug (Dietler, 2006). After being consumed by humans for millennia and having been the subject of psychological research for more than 150 years (Koelega, 1995), the psychoactive nature of alcohol as an intoxicant is well known. Whereas moderate alcohol consumption is reported to have positive effects on some aspects of physiological health (Sayed & French, 2016) and psychological well-being (Baum-Baicker, 1985; Müller & Schumann, 2011; Peele & Brodsky, 2000), consumption at higher doses is associated with a range of negative outcomes (Courtney & Polich, 2009; Wellman, Contreras, Dugas, O'Loughlin, & O'Loughlin, 2014). To reduce the prevalence of high levels of consumption, public health and safety campaigns often prescribe safe or responsible drinking practices (Measham, 2006), and guidelines for alcohol consumption are usually given in terms of prescribed doses. When determining safe doses, the strength of the drug's effect relative to the size of the dose, or the dose effect, is an important pharmacological factor that should be considered to provide accurate and appropriate guidance for safe consumption.

The strength of the effect produced by alcohol is generally dose dependent; that is, an increase in the dose of alcohol consumed generally causes an increase in the effects produced by the drug (Hart, Ksir, & Ray, 2013; Peterson, Rothfleisch, Zelazo, & Pihl, 1990; Pohorecky & Brick, 1988). However, the effects of alcohol on behavior cannot be reliably predicted from the dose alone because the dose effect for alcohol has been shown to vary, resulting in different strengths of effect from equally sized doses (Fillmore & Vogel-Sprott, 1998; Radlow, 1994). Changes in the dose effect are relevant to understanding the pharmacology of alcohol because they can confound efforts to predict the effects of alcohol at a given blood alcohol concentration (BAC), to estimate the BAC from the effects, or to produce desired effects from a dose. Increases and decreases in the dose effect are referred to as sensitization and tolerance, respectively.

When tolerance occurs, a given dose of alcohol yields weaker effects relative to previous doses of the same size, and larger doses are needed to produce the effects of a similar magnitude (Vogel-Sprott & Sdao-Jarvie, 1989). Tolerance can be classified by the time frame in which the decrease in dose effect is observed (Kalant, 1996). Chronic tolerance results from exposure to alcohol over an extended period of time and can be observed between doses (Martin & Moss, 1993). After cumulative doses, the effect produced by a given dose of alcohol is seen to be less than the one that was produced by earlier doses of equivalent size; this is chronic tolerance. Alternatively, a decrease in the dose effect

within a shorter time frame is acute tolerance. In contrast to chronic tolerance, acute tolerance is not a decrease in the dose effect relative to previous doses but is observed within the duration of a single dose of alcohol (Rigter & Crabbe, 1980; Tabakoff, Melchior, & Hoffman, 1982). The rapid nature of the change in the dose effect makes acute tolerance very much relevant to our understanding of intoxicated behavior. Tolerance has been suggested to contribute to abusive alcohol use patterns and a more accurate conception of acute tolerance will likely aid our understanding of alcohol-use disorders (Beirness & Vogel-Sprott, 1984; Kalant, 1971, 1996).

The focus of this paper is acute behavioral tolerance, which is, specifically, a reduction in the effect of alcohol on behavior. Despite the effect also being reported in animal studies, this review is focused on acute behavioral tolerance in human samples specifically because the nature and significance of the effect of alcohol is especially unique in humans. Behavioral tolerance can be contrasted with tolerance observed at different levels of biological complexity, for example, molecular, cellular, and metabolic (Pietrzykowski & Treistman, 2008; Wilson, Erwin, & McClearn, 1984). As the spectrum of alcohol's effects includes behavioral impairment, a reduction in impairment is often used as evidence of a diminished dose effect. Because the BAC is the temporal unit of dose, acute tolerance can be shown within the time course of a single dose by a decrease in the effect of alcohol relative to the BAC. Evidence of acute tolerance comes from research paradigms that measure the effects of alcohol at multiple points during the time course of a dose while controlling for changes in BAC using computational methods or specific data (Martin et al., 1993). Because this can be done in a multitude of ways, numerous different paradigms have been used to examine changes in the dose effect within the duration of a dose.

The primary aim of this review is to identify where empirical evidence of acute tolerance has been found by examining and comparing findings from the different paradigms that are appropriate for testing the effect. The most commonly used research paradigm for examining acute behavioral tolerance is that which was used by Mellanby (1919), who first reported an acute tolerance effect. The time course of the BAC produced by a single dose of alcohol reliably follows a two-limbed curve, initially rising quickly from baseline to peak and then declining less quickly back to baseline (Posey & Mozayani, 2007; Watson, Watson, & Batt, 1981). The Mellanby paradigm controls for changes in BAC by comparing between measures from two time points during the dose, with equivalent BACs (Crow & Batt, 1989): once when BAC is ascending and again when BAC is descending (see Figure 4). Mellanby observed that dogs showed less ataxia (involuntary movement such as swaying) on the descending

limb of the BAC curve compared with the ascending limb (Ferner, Holland, Sullivan,& Dufol, 2016). A decrease in dose effect observed between the ascending and descending limbs of the BAC curve is commonly referred to as the Mellanby effect.

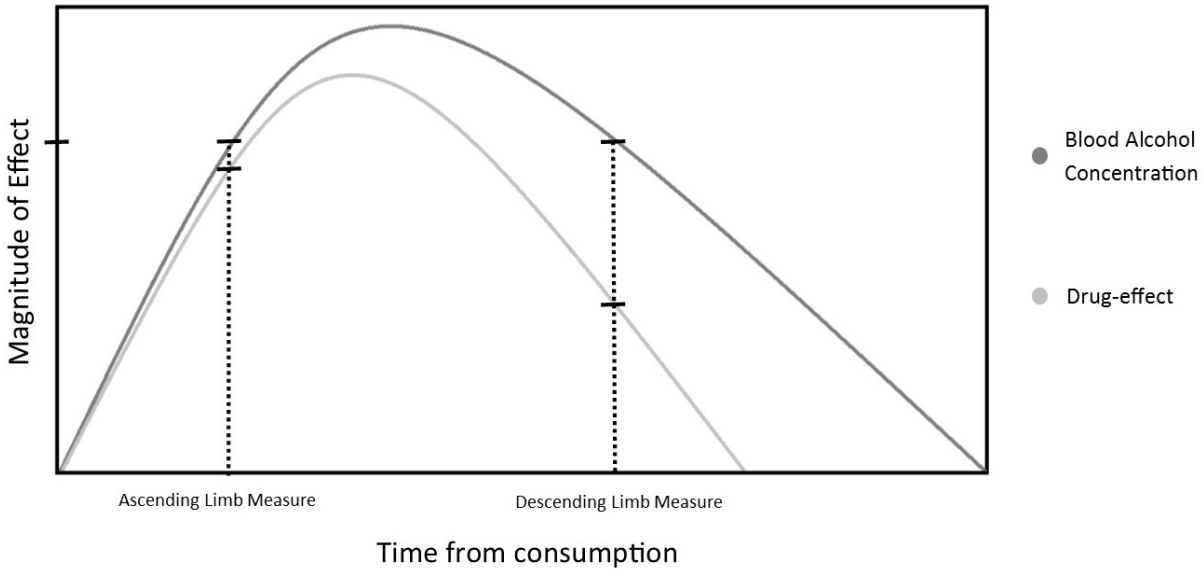


Figure 4. Blood alcohol concentration versus drug-effect during a single dose of alcohol showing the Mellanby effect.

Although the Mellanby paradigm has been the most popular method of examining acute tolerance, other paradigms have been used to model changes in the dose effect during the course of a single dose of alcohol. Each paradigm has certain limitations and advantages. An inherent confound in the Mellanby paradigm is that it is unable to control for differences in the direction of BAC change between each limb of the BAC curve (Rigter et al., 1980). A comparison of dose effect at equal BACs within the time course of a single dose necessitates measures being taken when the BAC is increasing and decreasing. Although the paradigm is a valid method of examining changes in the dose effect, it is unable to differentiate between those decreases that are dependent on the direction of BAC change and those that are not. Previous reviews on the topic of acute behavioral tolerance have been limited to studies that used the Mellanby paradigm (Holland & Ferner, 2017; Schweizer & Vogel-Sprott, 2008), which restricts the conclusions that can be drawn to the limitations of the paradigm. Paradigms other than Mellanby's have the potential to overcome these limitations and provide unique and additional evidence for acute tolerance. The present review is distinct in its inclusion of examinations of acute behavioral tolerance outside the Mellanby paradigm. By including other paradigms, a larger, more diverse sample of studies can be examined, and a more comprehensive understanding of acute tolerance may be achieved.

The second aim of this review is to identify the different domains of behavior in which acute tolerance has been shown to occur. Research has shown that some tasks seem to show more susceptibility to acute tolerance than others (Ginsburg, Martinez, Friesenhahn, Javors, & Lamb, 2008), and studies do not consistently find acute behavioral tolerance in any or all measures tested. As a result, it has been suggested that acute tolerance does not occur uniformly across behavioral domains (Schweizer et al., 2008). A range of different behavioral measures have been used to examine which specific facets of behavior show changes in the dose effect of alcohol, but it remains unclear which domains of behavior are susceptible to the effect. Furthermore, it has been suggested that findings of acute tolerance on particular measures vary between studies because the development of acute behavioral tolerance depends on numerous factors. These include the dose of alcohol administered and the task used to measure its effects (Rigter et al., 1980). The third aim of this review was to ascertain what conditions, if any, have been found to influence the development of acute tolerance.

To achieve these aims, the findings of the review are structured in the following way; first, the various paradigms identified as suitable for testing acute tolerance are detailed, and the merits and limitations of each are discussed; second, findings of acute tolerance in subjective and objective domains of behavior are examined, and the variability of the effect, both between and within measures, is considered; finally, the influence of dosing procedures and the significance of special populations is addressed.

Method

This review is limited to studies examining the dose-effect of alcohol on human behavior. Although acute alcohol tolerance has also been examined in other domains, including neurological and physiological measures, restricting the scope of this review to the effect in behavioral measures was considered appropriate for the sake of specificity. Acute behavioral tolerance in animals has been examined in numerous studies (Ginsburg et al., 2008; LeBlanc, Kalant, & Gibbins, 1975), but these were not included because the nature of alcohol effect in humans is not comparable with the effect in animals. Because this was a review paper and no new data were collected, approval from an institutional review board was not sought.

Prior to commencing the literature search (see Figure 5), the following criteria were determined as appropriate to filter the search results to meet the aims of the review. Publications were

included if they were published in the 50-year period between January 1967 and December 2017 in an English-language peer reviewed journal, reported the effect of alcohol on at least one behavioral measure, used human subjects, and reported appropriate statistics to test for acute tolerance.

The Scopus database was initially searched using the terms “acute tolerance” and “alcohol”. Seven articles were selected from their titles and screened against the eligibility criteria. These publications were used as the basis for a second search for publications that had been referenced by these first seven articles or had referenced these seven publications (a backward and forward search). The results from the second search were then used to identify additional search terms, which were mapped onto a logic grid (see online supplementary material) for four different databases (Embase, PsycINFO, PubMed, and Scopus). The initial and subsequent search terms were used to conduct a comprehensive search of the Embase, PsycINFO, PubMed, and Scopus databases. This search strategy was intended to be broad enough to include eligible articles that did not specifically report acute tolerance.

The comprehensive search of four databases yielded 10,446results, including 4,551 duplicate articles that were removed. The titles of the remaining 5,895 articles were screened; of these, 5,070 were excluded for being not relevant to acute alcohol tolerance, being outside the publication date range, or not testing human subjects. The abstracts of the 825 remaining articles were then screened against the eligibility criteria, after which 268 articles remained. The full text of these 268 articles were screened, which resulted in a further 218 articles being excluded for not reporting appropriate statistics to test for acute tolerance or not examining the effect in human behavior. A final sample of 50 articles was included for review. This included four articles with overlapping samples from two different studies. From the 48 individual studies that were included for review, data were extracted and tabulated regarding dose, consumption time, relevant BAC data, paradigm used to test acute tolerance, behavioral domain(s) examined behavioral measures tested, and finding of acute tolerance (Table 2 and Table 3). Analysis of demographic data was included and is detailed at the end of the results.

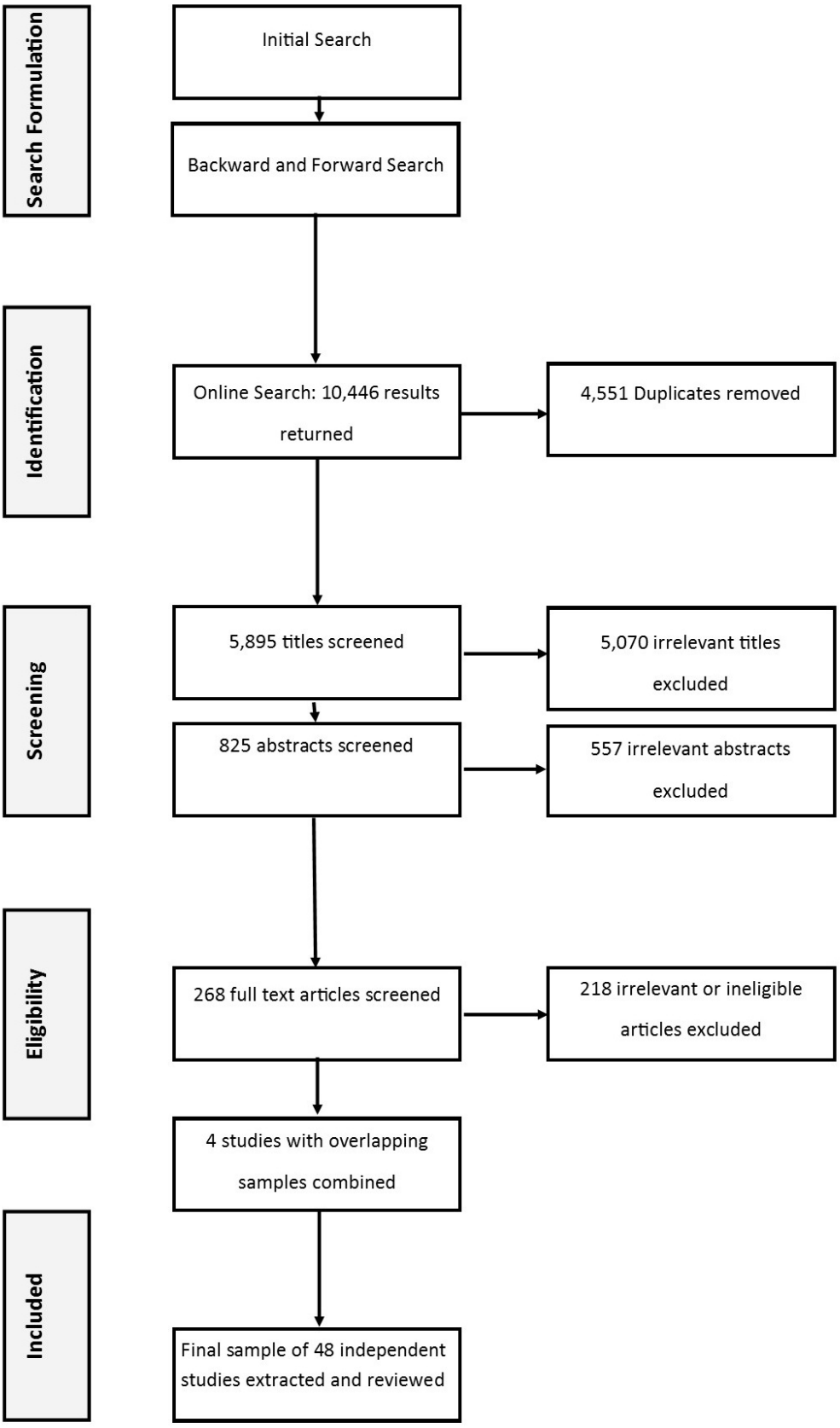


Figure 5. Flow chart of the study selection process.

Table 2.
Details of Studies Using Mellanby Paradigm

	Reference Author(year)	Dose (g/kg)	Consumption time (minutes)	Peak BAC (gm%)	BAC on ascending limb	BAC on descending limb	Domain	Measure	AT Found
1)	Amlung et al. (2014)	0.74(m) 0.65(w)	7	NR	0.068 at 31	0.067 at 124	Subjective	Perceptions of dangerousness	Yes
							Subjective-perceptions of driving	Willingness to drive	Yes
							Subjective-intoxication	10-point scale	Yes
2)	Bennett et al. (1993)	0.75 , 1.0	45	NR	Multiple	Multiple	Psychomotor	Videogame performance	No
							Subjective-intoxication	estimated number of drinks	No
							Subjective-intoxication	10-point scale	No
3)	Cash et al. (2015)	NR	105	0.07	0.05 at 40	0.05 at 190	Subjective-intoxication	3x 10-point scales	No
	Peacock et al. (2015)						Psychomotor-hand eye coordination	Compensatory tracking task	No
							Cognitive-information processing	Digit symbol substitution task	No
							Cognitive-response inhibition	Brief stop signal task	No
							Cognitive-information processing	Inspection time	No
4)	Cromer et al. (2010)	0.69	Varied	0.01	0.02, 0.04, 0.06, 0.08, 0.1	0.02, 0.04, 0.06, 0.08, 0.2	Cognitive-ECF	Groton maze learning task	Yes
							Subjective-intoxication	VAS	Yes
5)	Davis et al. (2009)	0.82(m), 0.68(w)	9	0.08	0.073 at NR	0.072 at NR	Subjective-intoxication	10-point scale	Yes
6)	Dougherty et al. (1998)	1.05	120	0.11	Multiple	Multiple	Psychomotor	Pursuit rotor task	No
7)	Earleywine (1995)	0.5	25	0.05	0.035 at NR	0.035 at NR	Subjective-affect	Biphasic alcohol effect scale	Yes
8)	Earleywine & Erblich (1996)	0.5, 0.8	20	0.053, 0.076	0.042, 0.062 at NR	0.038, 0.075 at NR	Subjective-affect	Biphasic alcohol effect scale	Yes
9)	Fillmore et al. (2000)	0.56	7	0.066	0.061 at 37	0.059 at 70	Cognitive-selective attention	Colour naming reaction time task	Yes
10)	Fillmore et al. (2005)	0.65	6	0.083	0.071 at 30	0.07 at 90	Cognitive-response inhibition/activation	Cued go/no go task	Yes
							Subjective-affect	Biphasic alcohol effect scale	Yes
							Subjective-intoxication	Estimated number of drinks	Yes
11)	Fillmore & Weafer (2012)	0.65	6	0.071	0.054 at 30	0.057 at 90	Cognitive-response inhibition/activation	Cued go/no go task	Yes
							Psychomotor	Grooved pegboard	Yes
							Subjective-intoxication	VAS	Yes
12)	Gengo et al. (1990)	0.48, 0.69, 0.96	180	0.065, 0.102, 0.129	Multiple	Multiple	Cognitive	Digit symbol substitution task	No
							Cognitive-reaction time	Choice reaction time	No
							Psychomotor	Simulated driving performance	No
							Subjective-intoxication	VAS	Yes
13)	Giancola & Zeichner (1997)	0.9	20	0.11	0.081 at 46	0.08 at 177	Misc	Taylor aggression paradigm	Yes
							Subjective-affect	Biphasic alcohol effect scale	Yes
14)	Grattan-Miscio & Vogel-Sprott (2005)	0.62(m), 0.54(w)	7	0.086	0.068, 0.08	0.064, 0.073	Cognitive-working memory	Sternberg memory scanning task	Yes
15)	Hiltunen (1997)	0.5, 1.0	45	NR	Multiple	Multiple	Cognitive	Pauli test	Yes
							Psychomotor	Pursuit rotor task	Yes
	Hiltunen (1997)						Subjective-intoxication	VAS	Yes
16)	Jones (1973)	1	15	0.11	0.09 at NR	0.09 at NR	Cognitive-memory	Verbal free recall	Yes
17)	Jones & Vega (1972)	1	15	0.11	0.09 at NR	0.09 at NR	Cognitive	Shipley Institute of living Scale	Yes
							Misc	Maudsley personality inventory	Yes
18)	Marczinski & Fillmore (2009)	0.65	6	0.08	0.075 at 90	0.075 at 120	Psychomotor	Simulated driving performance	No
							Subjective	Willingness to drive	Yes
							Subjective-intoxication	Estimated number of drinks	Yes
19)	Martin et al. (1991)	0.565	10	0.075	0.06 at NR	0.06 at NR	Subjective-intoxication	10-point scale	Yes
20)	Miller & Fillmore (2014)	0.65	6	0.075	0.059 at 30	0.061 at 90	Cognitive-response inhibition/activation	Cued go/no go task	No
							Cognitive-reaction time	2-choice reaction time	Yes
							Psychomotor	Grooved pegboard	Yes
							Subjective-intoxication	VAS	Yes
21)	Morris et al. (2014)	0.72(m), 0.65(w)	15	NR	0.072, 0.071 at NR	0.071, 0.076 at NR	Subjective	Perceptions of dangerousness	Yes
							Subjective	Willingness to drive	
22)	Nicholson et al (1992)	NR	20, 40	NR	.06 at NR	.06 at NR	Psychomotor-reaction & anticipation time	Bassin anticipation timer	Yes
							Misc	Far and near acuity	No
							Misc	Depth perception	Yes

	Reference Author(year)	Dose (g/kg)	Consumption time (minutes)	Peak BAC (gm%)	BAC on ascending limb	BAC on descending limb	Domain	Measure	AT Found
23)	Ostling & Fillmore (2010)	0.65	6	NR	0.075, 0.084 at NR	0.081, 0.08 at NR	Cognitive-response inhibition/activation	Cued go/no go task	Yes
							Psychomotor	Grooved pegboard	Yes
							Subjective-intoxication	VAS	Yes
24)	Pihl et al. (2003)	1	20	0.099	0.08 at NR	0.08 at NR	Cognitive-ECF	Random object span task x4	No
							Cognitive-ECF	Acquired spatial association task	No
							Cognitive-ECF	Acquired non-spatial association task	No
							Subjective-intoxication	Profile of mood states	No
25)	Pishkin et al. (1983)	1	15	NR	0.08 at NR	0.09 at NR	Cognitive-information processing	Concept identification	No
26)	Savoie et al. (1988)	0.58	15	0.085	0.059 at NR	0.058 at NR	Psychomotor	Grooved pegboard	No
							Psychomotor	Finger tapping speed	Yes
							Subjective-affect	Multiple affect adjective checklist	Yes
27)	Schweizer et al. (2004)	0.65	6	0.1	0.075 at 42	0.084 at 100	Cognitive-information processing	Psychological refractory paradigm	Yes
28)	Schweizer et al. (2006)	0.65	6	0.096	0.081 at 35	0.079 at 90	Cognitive-memory	Immediate word discrimination	No impairment
							Cognitive-memory	Delayed word discrimination	Yes
							Cognitive-memory	Immediate design memory	No
							Cognitive-memory	Delayed design memory	No
							Cognitive-working memory	X's & O's	No
							Cognitive-information processing	Symbol match with key	Yes
							Cognitive-memory	Symbol match without key	Yes
							Cognitive- response inhibition	Colour match	Yes
							Cognitive-working memory	Three letters	No impairment
29)	Soderlund et al. (2005)	0.78	95	0.08	0.03, 0.06 at NR	0.03, 0.06 at NR	Cognitive-memory	Associative learning	Yes
							Cognitive-memory	Picture recognition	No impairment
							Cognitive-memory	Word fragment completion	Yes
							Cognitive-memory	Free recall	No
							Subjective-affect	Profile of mood states	Yes
30)	Starkey & Charlton (2014)	0.75, 1.0(m), 0.6, 0.75(w)	10	NR	0.056, 0.094 at NR	0.053, 0.092 at NR	Cognitive-ECF	Groton maze learning	No
							Psychomotor	Simulated driving performance	No
							Subjective	Willingness to drive	Yes
							Subjective-intoxication	Visual analogue scale	Yes
31)	Streufert et al. (1992)	NR	180	0.047, 0.100	0.049, 0.077 at 30	0.031, 0.077 at 240	Cognitive	Digit symbol substitution	Yes
							Psychomotor	Videogame	No
32)	Vogel-Sprott & Chipperfield (1987)	0.65	45	0.079	0.063 at NR	0.063 at NR	Psychomotor	Bead stringing	Yes
							Psychomotor	Hand steadiness	No
							Subjective-intoxication	Subjective high assessment scale	Yes
33)	Wang et al. (1993)	1.23	30	0.1	0.05, 0.075 at NR	0.05, 0.075 at NR	Psychomotor	Proprioception	Yes
34)	Weafer & Fillmore (2012)	0.65	6	0.094	0.072 at 35	0.073 at 90	Cognitive-response inhibition/activation	cued go/no go task	No
							Psychomotor	Grooved pegboard	Yes
							Psychomotor	Simulated driving performance	No
							Subjective	Willingness to drive	Yes
							Subjective-intoxication	VAS	Yes

Table 3.
Details of Studies Using Other Paradigms

	Reference Author(year)	Dose (g/kg)	Consumption time (minutes)	Peak BAC (grams%)	Details of Paradigm	Behavioural Domain	Measure	AT Yes/No
Steady State								
1)	***Fagan et al. (1994)***	*NR*	*300*	*0.094*	*Measures every 20 min during plateau*	*Psychomotor*	*Postural sway*	*No*
						Psychomotor	*Finger tapping speed*	*No*
						Cognitive	*Digit symbol substitution*	*No*
						Subjective-intoxication	*VAS x6*	*No*
2)	***Hendershot et al. (2015)***	*Clamped infusion*	*Plateau at 20 min*	*0.08*	*Go/no go administered at 40 & 90 min during plateau*	*Cognitive- response inhibition/activation*	*Cued go/no go task*	*No*
					BAES administered 3 times	*Subjective-affect*	*Biphasic alcohol effect scale*	*Yes*
3)	***Hiltunen et al. (2000)***	*Clamped infusion*	*Plateau at 60 min*	*NR*	*Measures at 40 & 120 min of plateau*	*Psychomotor-reaction time*	*Reaction time*	*No*
						Cognitive-reaction time	*2 choice reaction time*	*No*
						Cognitive-response inhibition	*2-choice RT with response inhibition*	*Yes*
4)	***Kaplan et al. (1985)***	*NR*	*360*	*0.1*	*Measures at 40, 120, 180, 240, 300 & 360 min of plateau*	*Psychomotor*	*Postural sway*	*No*
						Psychomotor	*Manual tracking*	*No*
						Cognitive-memory	*Short term word recall/recognition*	*No*
						Subjective-intoxication	*VAS*	*No*
5)	***Kosobud et al. (2015)***	*Clamped infusion*	*Plateau at 19 min*	*0.06*	*Measures at 5 & 105 min of plateau*	*Subjective-intoxication*	*VASx7*	*Yes*
6)	***Morzorati et al. (2002)***	*Clamped infusion*	*Plateau at 20 min*	*0.06*	*measures at 5 & 85 min of plateau*	*Subjective-affect*	*Biphasic alcohol effect scale*	*Yes*
			-			*Subjective-intoxication*	*Sensation scale*	*No*
						Subjective-intoxication	*VAS*	*Yes*
7)	***O'Connor et al. (1998)***	*Clamped infusion*	*Plateau at 45 min*	*0.05*	*Measures at 0, 25, 60 & 85 min of plateau*	*Subjective-intoxication*	*Shuckits subjective high assessment scale*	*Yes*
Peak Comparison								
1)	***Ellinwood (1981)***	*0.5, 0.8, 1.2*	*40*	*NR*		*Psychomotor*	*Wheel tracking*	*No*
						cognitive	*Digit symbol substitution task*	*No*
2)	***Radlow & Hurst (1985)***	*1*	*15*	*NR*		*Subjective-intoxication*	*Magnitude estimation*	*Yes*
Rate of Recovery								
1)	***Post et al. (1998)***	*0.78*	*40*	*NR*		*Psychomotor*	*Apparent concommitant motion*	*Yes*
						Psychomotor	*Vestibular-occular reflex*	*No*
2)	***Vogel-Sprott & Fillmore (1993)***	*0.55*	*40*	*0.078*		*Psychomotor*	*Tracometer*	*Yes*
Onset/Offset								
	Haubenreisser & Vogel-Sprott (1987)	*0.6*	*41*	*68.2, 74.9*	*Onset/offset = 1SD from drug free performance*	*Psychomotor*	*Tracometer*	*No*
Hysteresis curve								
	Tupler et al. (1995)	*0.4, 0.6, 0.8, 1*	*10*	*0.055, 0.079, 0.11, 0.14*		*Psychomotor*	*Sub-critical tracking*	*No*
						Psychomotor	*Keypad reaction time*	*No*
						Cognitive	*Digit symbol substitution task*	*Yes*
Carry-over								
	Benton et al (1982)	*NR*	*5*	*0.03, 0.04*	*Repeat dose given when first had subsided*	*Subjective-intoxication*	*Magnitude estimation*	*Yes*

Many articles returned in the literature search reported an acute tolerance effect but were subsequently excluded because they did not report the appropriate statistics to test for acute tolerance. Fourteen of these studies used an ineligible form of the Mellanby paradigm, whereby measures were taken at a higher BAC on the ascending limb and a lower BAC on the descending limb. The data from this paradigm were considered ineligible because the reported decrease in the dose effect is too easily confounded with the change in the BAC (Schweizer et al., 2008). Five other studies that reported an acute tolerance effect were excluded because they did not report the BACs at which measures were administered. For observations of dose effects to be meaningful, it is necessary to report the BAC at the time of drug-effect measures (Jellinek &McFarland, 1940). This is especially true in acute tolerance research to observe a change in the dose effect. In the following sections, we refer to a wide range of different behavioral measures. In each case we provide only a brief description of the measure (e.g., a psychomotor task, a short-term memory task, etc.). For full descriptions of the tasks, we refer the reader to the original sources.

Results

Thirty-nine of the 48 studies included in this review found evidence of acute tolerance on at least one of the behavioural measures used in the study. Seven different research paradigms appropriate to examine acute tolerance were identified from the sample of studies reviewed. Each of the different paradigms produced evidence of acute behavioral tolerance in at least one study. These will be outlined in turn.

Paradigms

Mellanby.

The Mellanby paradigm was the most commonly used method for examining acute behavioral tolerance. The popularity of the paradigm is likely due to its practicality and simplicity because it can control for changes in BAC and show changes in the dose effect using relatively few data points. Thirty-four studies used the Mellanby paradigm, of which 28 found evidence of acute tolerance in at least one measure. The paradigm was able to find evidence of acute tolerance across dose sizes ranging from 0.48 g/kg to 1.23 g/kg. The BAC at which the dose effect was measured on each limb ranged from 0.036% to 0.09%. Only six of the studies that used the Mellanby paradigm did not find acute tolerance on any measure used to test for the effect. Notably, the doses given in four of these studies had longer consumption times than in other studies, which did find acute tolerance using the

same measures (Bennett, Cherek, & Spiga, 1993; Cash, Peacock, Barrington, Sinnett, & Bruno, 2015; Dougherty, Bjork, & Bennett, 1998; Peacock, Cash, & Bruno, 2015). In these four studies, the dose was split and administered over an extended period. As a result, the measures of drug effect on the ascending limb of the BAC curve were taken before the entire dose had been consumed. Thus, whereas drug effects were compared between equal BACs, the total amount of alcohol consumed varied between measures, such that measures taken on the descending limb of the BAC curve were compared with measures taken under the effect of a smaller dose. Although this split-dose protocol was able to show acute behavioral tolerance in some studies (Gengo, Gabos, Straley, & Manning, 1990; Söderlund, Parker, Schwartz, & Tulving, 2005; Streufert et al., 1992), studies with faster consumption times were more likely to find the effect.

Only two studies with short consumption times did not find acute behavioral tolerance using the Mellanby paradigm. Neither the measures of information processing ability (concept identification task) tested by Pishkin, Lawrence, and Bourne (1983) nor the measures of executive cognitive functioning (random object span task, acquired spatial association task) used by Pihl, Paylan, Gentes-Hawn, and Hoaken (2003) showed acute tolerance. Notably, these measures were not used in any other study. However, the Profile of Mood States used by Pihl et al. (2003) to measure changes in affect did show acute tolerance when tested by Söderlund et al. (2005) under a smaller dose.

In the Mellanby paradigm, both the dose given and the BAC at the time of measurement determine how much time is elapsed between the ascending and descending limb, and this may influence whether acute tolerance is observed (Martin et al., 1993). As an example, Miller and Fillmore (2014) and Savoie, Emory, and Moody-Thomas (1988) examined acute tolerance in grooved pegboard performance by comparing the effect of alcohol on task performance at approximately 0.06% on each limb of the BAC curve. Miller et al. (2014) reported that performance on the task was less impaired on the descending limb. However, Savoie et al. (1988) did not find the same pattern of effect after a lower dose (0.58 g/kg vs. 0.65 g/kg), in which less time elapsed between measures tested at 0.06% on each limb. These subtle variations in the details of the paradigm limit the comparisons that can be drawn between the studies that use it.

The methodology of studies using the Mellanby paradigm also varied in how the timing of measures on each limb was determined. Some studies continuously monitored participants' BAC through the course of the dose and administered measures contemporaneously, with breath alcohol readings reaching a particular BAC on each limb (Davis et al., 2009; Giancola, 1997). Others

administered measures at a prescribed time that coincided with a particular BAC (Marczinski & Fillmore, 2009; Schweizer, Jolicoeur, Vogel-Sprott, & Dixon, 2004). Strategies for matching BAC also included interpolating performance at specific BACs from multiple measures on each limb (Cromer, Cromer, Maruff, &Snyder, 2010) and comparing pairs of measures with the least difference in BAC from multiple data points (Hiltunen, 1997a, 1997b; Morris, Treloar, Niculete, & McCarthy, 2014).

Another source of variance between studies using the Mellanby paradigm was how the dose effect was compared between limbs. Most commonly, raw or difference scores were compared between each limb of the dose curve. These comparisons were made either between or within subjects. However, some studies did not directly compare the drug effect between limbs but used the absence of an impairment on the descending limb after the presence of an impairment on the ascending limb as evidence of acute behavioral tolerance. Presence of an impairment was also qualified in different ways: either as a difference from baseline performance or by comparison with a placebo group. Again, comparisons between studies that used the Mellanby paradigm are limited by these inconsistencies.

Steady-state.

In the steady-state paradigm (see Figure 6), the BAC is held constant at a predetermined concentration. Steady-state conditions can be established by giving an initial loading dose to reach the prescribed BAC and then using small oral doses or continuous intravenous infusions to maintain it. Measures of the effect of alcohol are then taken several times while BAC is held constant. If the effect of alcohol is seen to decrease, this can be attributed to a decrease in the dose effect because the dose (BAC) is not changed. An advantage of the steady-state paradigm is that the potential influence of the rate of BAC change and BAC change direction is controlled for.

This review identified seven studies that used a steady-state paradigm and five found evidence of acute behavioral tolerance. Two studies maintained a constant BAC by giving an initial oral dose to reach the desired BAC and then repeatedly giving oral maintenance doses throughout, but neither reported acute tolerance occurring on any measure (Fagan, Tiplady, & Scott, 1994; Kaplan, Sellers, Hamilton, Naranjo, & Dorian, 1985). The remaining five studies using the steady-state paradigm maintained a constant BAC through means of an intravenous clamp. Clamping adjusts the infusion rate of intravenously administered alcohol to match the elimination rate, enabling a prescribed BAC to be reached and maintained for an extended duration. This controls for several pharmacokinetic factors that can produce variation in BAC between individuals. All five of the studies that used an intravenous clamp found evidence of acute behavioral tolerance (Hendershot et al., 2015; Hiltunen,

Saxon, Skagerberg, & Borg, 2000; Kosobud et al., 2015; Morzorati, Ramchandani, Flury, Li, & O'Connor, 2002; O'Connor, Morzorati, Christian, & Li, 1998). The use of intravenous clamping has the advantage of being able to effectively and accurately establish steady-state conditions, but this comes at the cost of ecological validity; that is, the typical route of administration for alcohol consumption is oral, not intravenous. However, the findings from these studies provide substantial evidence of a decrease in dose effect independent of BAC change direction.

Peak comparison.

The peak comparison paradigm can show evidence of acute tolerance by comparing the times during a single dose of alcohol, at which the peak BAC and peak magnitude of effect occur (see Figure 6). As a dose of alcohol is absorbed and distributed through a body, the rise in BAC slows before peaking. When the BAC is increasing at a slower rate than the drug effect is decreasing, the magnitude of effect will peak and begin to decline. This causes an asymmetry between the BAC and effect in which the effect is seen to peak before the BAC does (Radlow &Hurst, 1985).

The peak comparison paradigm was used by two studies in this review, of which only one found evidence of acute behavioral tolerance. Radlow et al. (1985) reported that after a dose of 1 g/kg, the subjective intoxication produced by the dose peaked earlier and recovered faster than the BAC. This pattern was not found by Ellinwood, Linnoila, Easler, and Molter (1981), in which the peak effect from a dose of alcohol on a psychomotor task (wheel tracking) occurred after peak BAC. Because the drug effect is not compared between limbs, this paradigm also provides evidence of a decrease in the dose effect independent of BAC change direction.

Rates of recovery.

The rate of recovery paradigm examines changes in dose effect by comparing the rates at which the effect of alcohol and BAC decrease (see Figure 6), a faster recovery of effect than of BAC being indicative of acute tolerance. Measures of both drug effect and BAC are taken at multiple times after reaching their peak, thus, the effects on the ascending limb are not considered. If the drug effect relative to BAC decreases while BAC is decreasing, then the drug effect will decrease at a faster rate than BAC. By comparing the differences between BAC and drug effect over time, the rate of recovery paradigm is able to provide a measure of the rate that acute tolerance develops (Radlow, 1994).

Two studies demonstrated acute behavioral tolerance using the rates of recovery paradigm. Post, Tavano, and Maddock (1998) were able to quantify the development of acute tolerance to impairment of apparent concomitant motion (a measure of perceptual stability during head

movement) as 0.16%/min, meaning that per minute, impairment returned to baseline at a rate of 0.16% faster than BAC. Vogel-Sprott and Fillmore (1993) examined psychomotor performance (tracometer task) and found that the impairment from a 0.55 g/kg dose recovered twice as fast as the BAC did (-0.72% vs. -0.357%/min). By measuring rates of recovery, these two studies were able to show acute behavioral tolerance development over time, rather than just evidence of its occurrence. The difference in the rates of acute behavioral tolerance development between these two types of measures is consistent with the effect not occurring uniformly between domains.

Additional paradigms.

Three additional paradigms appropriate for examining acute behavioral tolerance were each used only in a single study. Haubenreisser and Vogel-Sprott (1987) found evidence of acute behavioral tolerance using an offset/onset paradigm, which examined changes in impairment relative to BAC during the dose by comparing the BAC at which impairment was and was not present. After administering a dose of 0.6 g/kg, psychomotor (tracometer) performance was measured at multiple time points. Impairment on the task was defined as a change from baseline performance of 1 *SD* or more. Indicative of a decrease in the dose effect, impairment was found to offset at a higher BAC than at the onset. However, given that the onset and offset occurred on differing limbs of the BAC curve, this method is vulnerable to the same limitations as the Mellanby paradigm.

One study (Tupler, Hege, & Ellinwood, 1995) found acute tolerance to performance impairment on the digit symbol substitution task (a cognitive speeded matching task), using an analysis of the dose effect time course with hysteresis curves. Hysteresis curves plot the time course of the dose against the BAC and dose effect. This allows the temporal changes in the dose effect to be examined and decreases consistent with acute tolerance to be observed.

Benton, Banks, and Vogler (1982) used a unique carry-over paradigm to show a decrease in the dose effect. Participants rated their feelings of intoxication throughout the duration of both a 0.65g/kg dose and a subsequent dose given when the initial dose had subsided. Relative to contemporaneous BAC, ratings of subjective intoxication given during the second dose were lower than those given during the prior dose. This was the only study to show the effect of acute tolerance on subsequent doses.

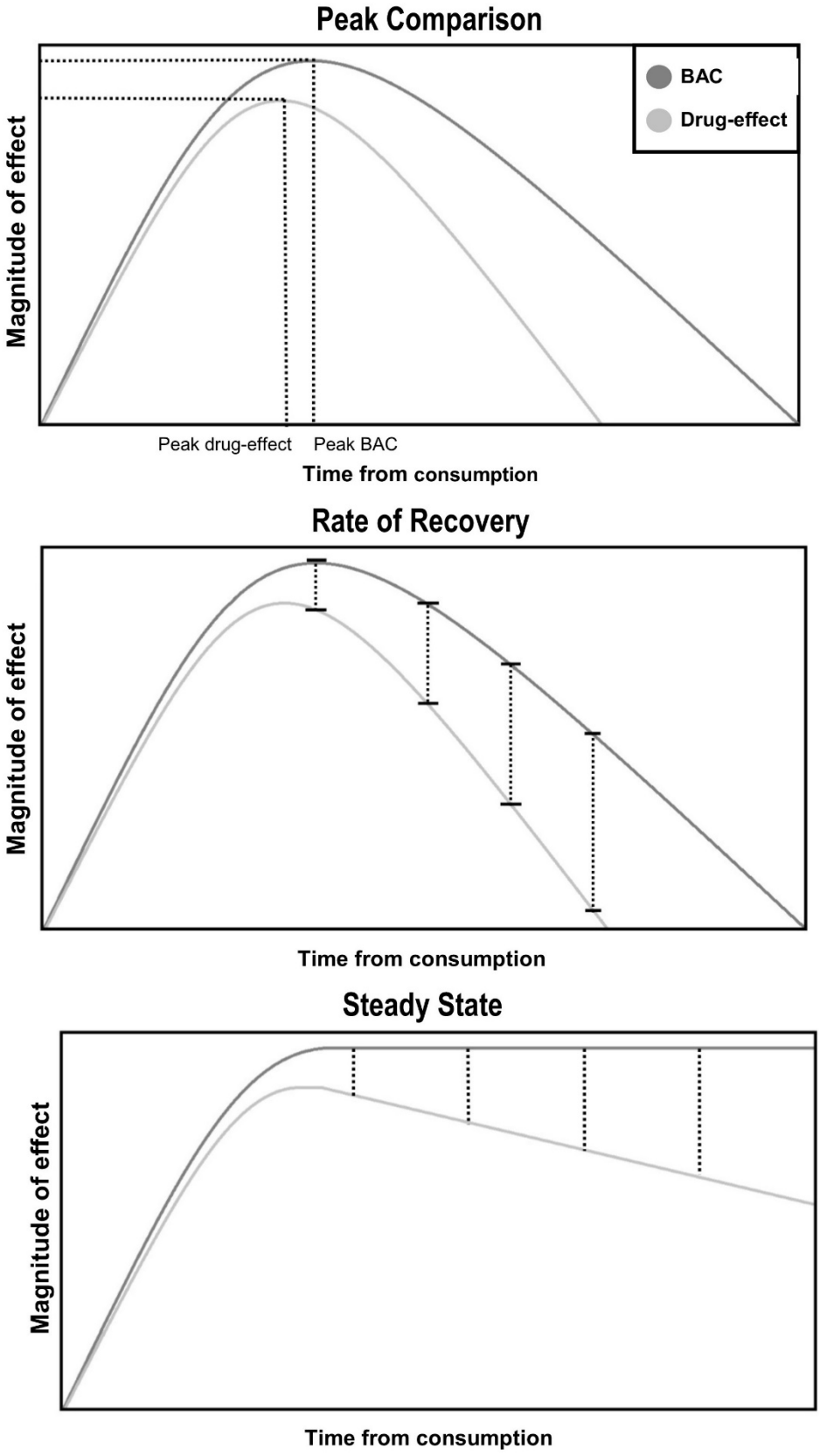


Figure 6. Demonstrations of acute tolerance in the Peak comparison, Rate of recovery and Steady state paradigms. BAC = Blood alcohol concentration.

Domains of Behavior

Across the various paradigms, 64 different behavioral measures were used to examine changes in dose effect. Of these, 37 showed acute behavioral tolerance in at least one study. Both subjective and objective measures were found to show acute tolerance, but the effect was most reliably seen in subjective measures, which use subjects' self-ratings to quantify the effects of alcohol. The subjective measures used in the studies reviewed can be further categorised as measures of subjective intoxication, affect, and perceptions of driving.

Subjective measures.

Subjective intoxication.

The most consistent evidence of acute behavioral tolerance that we found in this review was in relation to self-ratings of intoxication. Twenty-three studies used a measure of subjective intoxication, and acute tolerance to subjective intoxication was found in studies using the Mellanby, steady state, peak comparison, and carry-over paradigms. The only studies that measured subjective intoxication and did not find evidence of acute tolerance were those that used the split-dose protocol in a Mellanby paradigm, previously discussed. Six different types of subjective intoxication measures were used, but all were able to detect a decrease in the dose effect. All measures of subjective intoxication used one or more rating scales for subjects to contemporaneously self-report the level of intoxication or symptoms of intoxication they felt at the time of the measure. Visual analogue scales calculated as a percentage of the subject's maximum rating were used in 13 studies, of which nine showed acute tolerance. Point ratings on a fixed interval scale were used in 11 studies, and six showed acute tolerance. Other subjective intoxication measures used were the estimated number of drinks consumed, magnitude estimations, the subjective high assessment scale, and the sensation scale.

Perceptions of driving.

Five studies using a Mellanby paradigm found acute tolerance in measures of perceptions of driving. Subjects in the study by Weafer and Fillmore (2012) gave higher ratings of willingness to drive at 0.074% on the descending limb of a 0.65 *g*/kg dose. Marczinski et al. (2009) found binge drinkers were more willing to drive at 0.075% on the descending limb of a0.85 g/kg dose. Starkey and Charlton (2014) reported that subjects gave a higher willingness to drive ratings at 0.06% on the descending limb of a 0.75 g/kg dose, but ratings did not differ between limbs of a 1.0 g/kg dose at 0.09%. Amlung, Morris, and McCarthy (2014) found that at a BAC of 0.06%, 60% of subjects reported they were willing to drive on the descending limb, compared with 20% on the ascending limb, and

perceptions of dangerousness of driving were rated as lower when given on the descending limb (willingness to drive was found to be in part attributable to decreased perceptions of dangerousness). Morris et al. (2014) also measured perceived dangerousness of driving and similarly found that ratings were lower on the descending limb of the dose curve. These studies all show that the effect of alcohol on perceptions about driving can decrease, while BAC remains elevated.

Affect.

Three different subjective measures of affect were used in nine studies: The Multiple Affective Checklist, the Profile of Mood States, and the Biphasic Alcohol Effect Scale. Eight of these nine studies found evidence of acute tolerance to the effect of alcohol on affect. This decrease in dose effect was not found for all facets of affect however.

Savoie et al. (1988) measured affect with the Multiple Affective Checklist at approximately 0.059% on each limb of a 0.58 g/kg dose. Men with a family history of alcoholism gave lower ratings of anxiety on the ascending limb but returned to pre-dose levels on the descending limb. Ratings of depression showed no difference between limbs.

The two studies that used the Profile of Mood States to measure affect had differing results. Söderlund et al. (2005) compared measures during a 0.78 g/kg dose at BACs of 0.03% and 0.06% on each limb. Vigor scores were lower on the descending limb, whereas depression and fatigue scores were higher. In contrast, these differences in affect between ascending and descending BAC limbs were not found on the Profile of Mood States by Pihl et al. (2003) after a higher dose (1.0 g/kg).

Six studies measured changes in affect using the Biphasic Alcohol Effect Scale (BAES). The BAES is a 14-item scale consisting of adjectives describing the simulant and sedative effects that vary between the ascending and descending limb of the BAC curve (Martin, Earleywine, Musty, Perrine, & Swift, 1993). A consistent acute tolerance pattern was seen for stimulation ratings on the BAES in the four studies that used the Mellanby paradigm (Earleywine, 1995; Earleywine & Erblich, 1996; Fillmore, Marczinski, & Bowman, 2005; Giancola & Zeichner, 1997). In these studies, the subjective ratings of stimulation were lower on the descending limb at equal BACs, whereas ratings of sedation did not vary. Two studies tested for acute tolerance with the BAES in a steady-state paradigm, using an intravenous clamp to maintain a constant BAC. Morzorati et al. (2002) and Hendershot et al. (2015) both found a similar decrease in ratings of stimulation occurred when BAC was held at a constant level.

Objective Measures.

Objective measures of behavior were less reliable than subjective ratings in demonstrating acute tolerance and showed more variation between tasks and conditions. This pattern was consistent across paradigms. Objective measures were categorized as measures of either psychomotor or cognitive performance or as miscellaneous measures of behavior. Psychomotor measures are those tasks involving physical movements that require conscious mental activity. Twenty-four articles used at least one psychomotor measure, of which 13 showed acute tolerance. Nineteen different psychomotor measures were used, and eight showed acute tolerance. Cognitive measures gauge an individual's capacity for complex and dynamic psychological functions (e.g., reasoning, planning, organizing, and problem solving) independent of physical ability (Agarwal & Goedde, 2012). Thirty-three different measures of cognitive performance were used in 25 studies. In 17 studies, 16 different measures of cognitive performance showed acute tolerance. Objective measures that were considered neither psychomotor nor cognitive were categorized as miscellaneous. These measures were the Taylor Aggression Paradigm (Giancola et al., 1997), tests of perceptual vision (depth perception; Nicholson et al., 1992), and the Maudsley Personality Inventory (Jones & Vega, 1972); all showed acute tolerance.

Objective measures of performance in more complex tasks such as videogame performance or simulated driving were notably more resistant to acute tolerance than more simple measures. Despite this, there was no psychomotor or cognitive measure that showed acute tolerance as reliably as subjective measures because most of the objective measures were seldom used in multiple studies. Only four objective measures found acute tolerance in more than one study. The Grooved Pegboard Task, a psychomotor measure of visual motor coordination, showed acute tolerance in four of the five studies that used it. Tracometer performance showed acute tolerance in both studies that used it. The Digit Symbol Substitution Task showed acute tolerance in two of the five studies that used it. Three of the six studies that used the cued go–no go task to measure response inhibition and activation found acute tolerance on measures of reaction time (RT).

Several studies included in the review did not find acute tolerance on a particular measure because the measure was not affected by alcohol. For example, short-term verbal and immediate working memory was tested by Schweizer et al. (2006), but performance on these measures was not significantly impaired from a dose of 0.65g/kg. For recovery to be shown, there must be sufficient impairment from which to recover. Negative findings of acute tolerance are potentially the result of an

inadequate degree of impairment being examined with an insufficient potential for recovery or the use of insufficiently sensitive measures.

Differences Between Measures Within a Given Study

Twelve studies reported that acute tolerance did not occur uniformly between different behavioral measures. That is, acute tolerance was found on at least one measure but not on others. There was a reliable mixed effect in studies that tested simulated driving performance. No study that tested it found acute tolerance on simulated driving performance, but all found acute tolerance on subjective measures, and some found the effect on other objective measures. Weafer et al. (2012) found the effect in subjective intoxication, the Grooved Pegboard task, and willingness to drive but not on simulated driving performance or performance on the cued go/no-go task. Marczinski et al. (2009) reported acute tolerance for subjective intoxication and willingness to drive but not simulated driving performance in a sample of binge drinkers. Starkey et al. (2014) did not find acute tolerance for simulated driving performance or the Groton Maze Learning Test but did find the effect in measures of subjective intoxication and willingness to drive under a medium dose. Gengo et al. (1990) reported the effect only for subjective intoxication, whereas the Digit Symbol Substitution Task simulated driving, and Choice Reaction Time performance did not show acute tolerance. The absence of acute tolerance development in driving ability whereas subjective intoxication and other effects diminish is significant for the issue of drunk driving. The results of this review indicate that people are likely to think they have recovered from the deleterious effects of alcohol while their driving ability remains impaired.

Findings of acute tolerance were inconsistent across different measures of memory. All studies that examined acute tolerance to alcohol effects on memory performance used the Mellanby paradigm. Jones (1973) compared free recall memory performance between limbs at 0.09% and found that whereas immediate recall was less impaired on the descending limb, short- and long-term recall did not recover. Schweizer et al. (2006) found long-term verbal and declarative memory to be less impaired on the descending limb but not short- or long-term visual or short-term verbal memory. Söderlund et al. (2005) reported that after a dose of 0.78g/kg, associative learning and word fragment completion differed only from placebo during the ascending limb of the BAC curve, whereas free word recall showed no differences between limbs. Given the temporal nature of acute tolerance, a time-dependent performance measure like memory may not be suitable to test for acute tolerance.

Other cases of mixed effects provide further examples of how different measures vary in their susceptibility to acute tolerance. Both studies that reported acute tolerance developing to the impairment in performance on the digit symbol substitution task did not find the effect on other measures used. Streufert et al. (1992) reported the effect for digit symbol substitution task but not videogame performance, whereas Tupler et al. (1995) reported the effect for the digit symbol substitution task but not keypad reaction time or tracometer performance. Vogel-Sprott and Chipperfield (1987) found acute tolerance in bead-stringing performance and also subjective intoxication but not hand steadiness. Post et al. (1998) found acute tolerance on only one of two similar psychomotor measures, apparent concomitant action, but not vestibular ocular reflex (eye movements that counter head movement to stabilize gaze). Hiltunen et al. (2000) found a difference in acute tolerance occurring between a complex reaction time task and simpler two-choice reaction time task and a simple reaction time task. When BAC was clamped at a constant of 0.07%, only the complex task showed acute tolerance. In contrast, Miller et al. (2014) reported acute tolerance on the two-choice reaction time task as well as grooved pegboard performance and subjective intoxication but not on the cued go/no-go task when performance was compared at a BAC of 0.06% on each limb of the BAC curve of a 0.65 g/kg dose. The high degree of variability in acute tolerance between different measures supports the hypothesis that the effect does not occur uniformly between measures. However, given the differences in the nature of the measures, and the variability of methods used when testing them, it cannot be discerned which kinds of tasks are more susceptible to developing acute tolerance.

Differential Effects on Outcome Measures within a Single Task

Several studies reviewed used multifaceted objective measures that measured more than one type of performance within a single task. Acute tolerance was often found to vary within these tasks between the types of performance being measured, providing evidence that some aspects of task performance are more sensitive to acute tolerance than others. For example, there was a consistent difference in the development of acute tolerance between measures of speed and accuracy in cognitive tasks. Measures of speed (usually as RT) were often found to develop acute tolerance, whereas measures of accuracy (usually as errors) were found to be resistant to acute tolerance.

This differential effect for speed and accuracy was found on the cued go/no-go task in three of the six studies in which it was administered. Fillmore et al. (2005), Fillmore and Weafer (2012), and Ostling and Fillmore (2010) all found acute tolerance in measures of response activation (speed) but

not response inhibition (accuracy). Reaction time on the cued go/no-go task was less impaired on the descending limb of the dose curve relative to the descending limb at an equivalent BAC, whereas errors on the task showed no difference between limbs. However, no acute tolerance was found in any aspect of the cued go/no-go task by Hendershot et al. (2015), Weafer et al. (2012), or Miller et al. (2014).

This differential pattern of effect was also found within measures of executive cognitive function and information processing. The Groton Maze Learning Test is a multifaceted measure of executive function, which was used to examine acute tolerance in two studies. Cromer et al. (2010) found measures of visuo-motorspeed and visuospatial learning efficiency on the Groton Maze Learning Test showed less impairment on the descending limb of the dose curve than on the ascending limb. Impairment to higher order cognitive functions (accuracy) did not differ between limbs. No acute tolerance was found on any facet of the Groton Maze Learning Test by Starkey et al. (2014). Acute tolerance to impairment in information processing was measured by both Schweizer et al. (2004) and Schweizer et al. (2006), each using different tasks. In both studies, RT (speed) for information processing tasks at a given BAC was found to be less impaired on the descending limb of the BAC curve, whereas accuracy showed no such recovery. However, neither Pishkin et al. (1983) nor Cash et al. (2015) observed acute tolerance in measures of information processing. Acute tolerance was also seen to develop faster in speed (RT) than accuracy (errors) on a measure of working memory used by Grattan-Miscio and Vogel-Sprott (2005). These findings provide some evidence that measures of speed in cognitive tasks are more likely to show acute tolerance than measures of accuracy. This lasting impairment to accuracy on cognitive tasks has been previously referred to as acute protracted error (Schweizer et al., 2008). The difference in dose-effect changes between these two fundamental mechanisms of behavioral control raises the possibility that the underlying structures responsible for different aspects of cognitive performance are affected differently by acute tolerance.

Experimental and Demographic Conditions Affecting Acute Tolerance

The effects of dose and risk of alcoholism on acute tolerance were the only factors repeatedly examined in the sample reviewed. Findings across the dose protocols required for specific paradigms have been previously discussed, but several studies compared the effects between different size doses. The status of subjects as either at risk or not at risk of alcoholism in studies that investigated its effect was not determined on the basis of a pre-existing diagnosis but from measures of family history of alcohol use disorder and binge-drinking behavior.

Dose size.

Dose was not reported in a uniform way by all studies reviewed. Where possible, reported doses have been equated to grams per kilogram. Those doses reported only as designed to reach a specific peak were calculated from the reported peak using the Widmark formula. Twelve studies did not use a dose protocol from which grams per kilogram could be calculated, including five studies that gave intravenous clamped doses. The mean dose given in the articles reviewed was 0.74 g/kg (*SD* = 0.2). The effect was reported across the entire range of doses tested: 0.4 g/kg (Earleywine et al., 1996) to 1.23 g/kg (Wang, Nicholson, Mahoney, Li, & Perko, 1993). The mean peak BAC in the 36 studies that reported it was *M* = 0.09 (*SD* = 0.071, range = 0.03–0.13).

The effect of dose size on acute tolerance was not consistent in the six studies that examined it. Nicholson et al. (1992) found that anticipation time only showed the effect after a 2-oz. dose but not a 1-oz. dose. Streufert et al. (1992) found that the digit symbol substitution task showed only acute tolerance for a dose of 1.0 g/kg but not 0.5 g/kg. On the other hand, Starkey et al. (2014) found only the lower of two doses (0.75 g/kg for men and 0.6 g/kg for women vs. 1.0 and 0.75 g/kg) showed acute tolerance for measures of willingness to drive and subjective intoxication. Earleywine et al. (1996); Gengo et al. (1990), and Tupler et al. (1995) tested multiple doses but did not find an effect of dose on the development of acute tolerance.

Taken together, the findings of acute tolerance across a range of doses suggests that this effect can occur across a wide range of doses. However, the range of doses tested is likely well below those found in real-world scenarios, particularly in instances of binge drinking. Although it is reasonable to expect that acute tolerance would occur at higher doses, the evidence reviewed here can be generalized only so far; given this, an understanding of the effect at higher doses and in real-world scenarios is notably limited.

Risk of alcoholism.

Comparison between at-risk and non–at-risk groups revealed at-risk groups were more likely to show acute tolerance. Morzorati et al. (2002) found an effect of family history of alcoholism on acute tolerance when using a steady-state paradigm. Only those subjects who had a positive family history of alcoholism (either a first- or second-degree relative with alcoholism) rated their level of intoxication progressively lower while BAC was held at 60 mg%. Savoie et al. (1988) reported that men with a family history of alcoholism showed acute tolerance to the influence of alcohol on affect, whereas those with no family history did not. Marczinski et al. (2009) grouped subjects by risk of

binge drinking status using the Personal Drinking Habits Questionnaire, which measures recent drinking history, and found that only binge drinkers showed acute tolerance to subjective intoxication and perceptions of driving after a 0.65 g/kg dose. Fillmore et al. (2012) used the Personal Drinking Habits Questionnaire and the Alcohol Use Disorders Identification Test to determine binge-drinking status and observed that grooved pegboard performance (motor coordination)and RT (response activation) in the cued go/no go task improved between limbs only for those who qualified as binge drinkers. This greater tendency toward acute tolerance in subjects with higher recent drinking history was, however, not found by Hiltunen (1997a, 1997b).

Using the Mellanby paradigm, Hiltunen (1997a) found only light consumers showed acute tolerance to impairment on a psychomotor measure (pursuit rotor task) under a 0.5 g/kg dose. Both moderate and light consumers showed acute tolerance on the task under a 1.0g/kg dose, but light consumers showed recovery in more aspects of task performance. Light consumers also showed acute tolerance to impairment in general intellectual ability (Pauli Test). Acute tolerance to impairment in pursuit rotor performance was not reported by Dougherty et al. (1998), who used a comparable method but with no group comparison based on consumption patterns. Hiltunen (1997b) also reported that light consumers demonstrated an acute tolerance to subjective effects under both dose sizes, but moderate consumers showed only acute tolerance to subjective effects from the 1.0 g/kg dose. This pattern was not found by Martin, Rose, and Obremski (1991), who found no effect of family history of alcoholism on the development of acute tolerance to subjective intoxication.

Demographics.

The combined number of subjects from all studies included in the review was 1,846. The average sample size was 38.5 (*SD* = 31.9, range = 6–150). There was a notable difference between the number of men and women represented in the total sample: men, 67% (*n* = 1,242) versus women, 23% (*n* = 417). Three studies (10% of the total sample) did not report the gender composition of their samples (Ellinwood et al., 1981; Jones et al., 1972; Kosobud et al., 2015). The majority of studies (*n* = 26) tested an entirely male sample (*n* = 793), and when subjects from these studies and those who did not report gender were removed, gender representation was nearly equal (male = 52%, female = 48%). However, no gender differences in acute behavioral tolerance were reported in any study that tested for them (Ostling et al., 2010; Radlow et al., 1985; Savoie et al., 1988).

All but one article reported subject age (Radlow et al., 1985). Thirty-one studies reported the mean age of the sample (*M* = 24.6 years, *SD* = 4.37). Forty-two studies reported the age range of the

sample (*M* = 12.97 years, *SD* = 7.81). The only effect of age on acute behavioral tolerance was found by Tupler et al. (1995), in which elderly subjects (59–65 years) were found to show more acute tolerance on the digit symbol substitution task compared with younger subjects (22–29 years).

Discussion

The overall finding from this review was that evidence of acute behavioral tolerance is prevalent. This evidence has come from studies using a variety of different research designs, behavioral measures, and dose sizes. Given that previous reviews have been limited to studies that used the Mellanby paradigm (Holland et al., 2017; Schweizer et al., 2008), the inclusion of additional paradigms makes the present review the most comprehensive to date. Seven different research paradigms were identified and all demonstrated acute tolerance. Although the Mellanby paradigm was evidently the standard method of investigation, the additional paradigms provide evidence of acute tolerance occurring independent from BAC change direction. The decrease in dose effect was not uniform across behavioral measures and was found in some studies to show either no significant change, or at times a change in the opposite direction to that expected (i.e., acute sensitivity). Subjective measures of the effect of alcohol were reliable in demonstrating acute tolerance, regardless of the size of the dose or the paradigm used. The effect was most robust for ratings of subjective intoxication, which were measured with a variety of scales. Objective measures were less reliable, but the effect was still seen in more than half of these measures. The wide variability across different tasks and the limited cases of measures being used between studies make it difficult to determine precisely which domains of objective behavior are affected. However, there appears to be a tendency for more simple tasks to show the effect and for measures of speed in cognitive tasks to be more sensitive to acute tolerance than measures of accuracy. This review also found evidence for the rate of consumption influencing the development of acute tolerance and identified sources of variability in the Mellanby paradigm that limit the comparisons that can be drawn between the studies which used it.

The decrease in the dose effect between limbs of the BAC curve has often been attributed to the difference in direction of BAC change on each limb, or a limb effect. A number of excluded articles reported limb effects from Mellanby paradigms that did not compare the dose effect between equivalent BACs between limbs. The five studies that found evidence of acute behavioral tolerance using the steady-state paradigm conflict with the notion that the effect is solely due to limb effects

because a decrease in dose effect was able to be observed when there was no change in BAC. Likewise, the findings from the peak comparison paradigm used by Radlow et al. (1985) and the carry-over paradigm used by Benton et al. (1982) also provide evidence for acute tolerance independent of BAC change direction. Although the findings from these paradigms do not refute a role of BAC change in the strength of the dose effect, they provide evidence of acute tolerance independent of BAC change direction. The inclusion of multiple paradigms in this review also allowed for a robust demonstration of the variability in acute tolerance between different measures. This was especially apparent in the comparison of studies that used the rates of recovery paradigm, which showed the rate of acute tolerance development varied between different measures.

The effect of alcohol on affect is widely reported to be biphasic, with positive affect being more pronounced on the ascending limb and negative affect more pronounced on the descending limb (Pohorecky, 1978; Rueger, McNamara, & King, 2009). The findings of this review suggest a role of acute tolerance in this biphasic effect. Ratings of the positive affect produced by alcohol were often found to decrease between limbs when compared at equal BACs. This rapid decrease in positive affect was also found when BAC was held constant. Conversely, this pattern was not found for ratings of negative affect. The difference in acute tolerance between positive and negative affect results in a biphasic pattern because the initial increase in positive affect subsides whereas negative affect remains elevated. Because of this differential effect on mood, a consumer may imbibe to excess when attempting to alleviate negative affect and promote positive affect. Because the reinforcing positive affect is greater more recently after consumption, larger, more frequent doses would be required to produce the same degree of positive affect later in the dose (Lukas, Mendelson, & Benedikt, 1986; King, de Wit, McNamara, & Cao, 2011). The potential of a reduction in dose effect to promote higher consumption is recognized as a factor that may contribute to alcohol abuse and dependence (Fillmore et al., 2005; Treistman & Martin, 2009).

A large body of literature has reported on the link between those at risk of alcohol-use disorder and the differentiated effect on mood, but the role of acute tolerance in this relationship has received little attention. Differences in the dose effects of alcohol observed in people at risk for alcohol-use disorders potentially reflect differences in acute tolerance (Schuckit, 1984). People with a positive family history of alcohol-use disorder show increased sensitivity to the positive reinforcing effects of alcohol associated with the ascending limb but also show greater tolerance to the sedative effects associated with the descending limb (Erblich, Earleywine, Erblich, & Bovbjerg, 2003). In the

limited examinations of high-risk groups in this review, they displayed no difference in sensitivity to positive affect but were more likely than non–at-risk groups to show acute tolerance to subjective intoxication and impairment on objective measures. However, it must be considered that the group comparisons used in this review did not examine subjects diagnosed with alcohol-use disorder. Given the associations between alcohol-use disorder and acute behavioral tolerance, investigations into the effect in a clinical population would be of obvious benefit.

The reliable finding of acute tolerance to subjective intoxication also highlights the potential of a reduction in dose effect to promote excess consumption of alcohol. Although the perception of intoxication is influenced by an array of factors such as setting and expectations (O'Malley & Maisto, 1984; Vogel-Sprott et al., 1989; Wiers & Kummeling, 2004), subjective responses provide the closest access to the cues that influence drinking behavior within a drinking session. Because the divergence in the dose effect seen in the subjective effects of alcohol is likely to cause error in estimates of one's own contemporaneous intoxication and drinkers may choose when and how much to drink to reach or maintain levels of intoxication on the basis of their subjective state, a reduction in subjective effects can be seen as a likely contributor to excess consumption (Banks, Vogler, & Weissbach, 1979; Earleywine et al., 1996). If the subjective effects of alcohol become reduced within a drinking session, subsequent drinks within the session would have a reduced effect, potentially leading to an increased rate of consumption to experience a desired magnitude of effect (Aston & Liguori, 2013). Data from natural drinking environments have demonstrated that people are more likely to underestimate their level of intoxication after the consumption of more drinks, which is consistent with an acute tolerance effect (Clapp et al., 2006).

In the case of someone deciding whether it is safe to drive after drinking, acute tolerance to subjective intoxication may lead them to underestimate their current level of impairment (Courtney et al., 2009; Lipscomb & Nathan, 1980), leading to an increased willingness to drive or engage in other dangerous behavior (Oei & Morawska, 2004). Experimental data support the notion that risky behavior is more prevalent on the descending limb of the BAC curve (Bidwell et al., 2013). As seen in this review, the effect of alcohol on people's perceptions about driving decreases rapidly after consumption, such that people show greater willingness to drive at BACs above the legal driving limit in many countries while on the descending limb of the BAC curve. The general population is not aware that there is a disconnect between the rate at which the felt effects and the impairment from alcohol recover. An increased awareness of variability in the dose effect of alcohol can potentially reduce the

harmful consequences that result from alcohol consumption, and guidelines for responsible drinking should include strategies for managing such effects.

The consistent pattern of effect between subjective intoxication and simulated driving performance is alarming. Evidence of acute tolerance to impairment in simulated driving tasks was uniformly negative, whereas in the same studies ratings of subjective intoxication and perceptions of driving reliably showed acute tolerance. This resulted in subjects feeling as though they had recovered from the effects of alcohol, while their performance in simulated driving tasks remained impaired. Although simulated driving tasks are not perfectly analogous to real-world motoring, they do provide a derivative of the skill set required for driving, which can be tested under laboratory conditions (Irwin, Iudakhina, Desbrow, & Mc- Cartney, 2017). Autopsy data, which included measures of alcohol pharmacokinetics, have shown that fatal road accidents are far more common during the descending limb of the BAC curve in which acute behavioral tolerance is most evident (Lahti et al., 2014; Levine & Smialek, 2000). Approaches for dealing with drinking and driving and alcohol-related road accidents need to consider the influence that changes in the dose effect could be having, especially the difference in recovery between subjective intoxication and other domains of behavior.

The variability in the dose effect demonstrated by the findings of acute tolerance reported in this review is especially important for research into the effect of alcohol on behavior. Despite longstanding recommendations by Jellinek et al. (1940) to account for the limb of the BAC curve that measures are taken, most research into the effects of alcohol on behavior have not considered acute tolerance. Behavioral effects are commonly measured only in the early stages of the dose when BAC is ascending. Given the reliable variation in dose effect over the course of alcohol elimination, methods investigating the effects of alcohol would benefit from reporting or controlling for temporal changes in dose effect, like acute tolerance.

The general effects of alcohol have been shown to be influenced by the rate the dose is consumed, with faster consumption being associated with stronger effects (Jones & Vega, 1973; Moskowitz & Burns, 1976; Viken, Rose, Morzorati, Christian, & Li, 2003). When BAC is increasing, faster consumption generally results in a faster rate of BAC change. Martin, Balaban, and McBurney (2006) reported that subjective intoxication is more strongly determined by the rate of BAC change than the actual magnitude of BAC. In this review, acute tolerance was more reliably found in studies that used shorter consumption times. In an article not included in this review Martin and Earleywine (1990) compared the acute tolerance between two similar studies that had different dosing protocols.

Acute tolerance was found to develop only in the study that had the faster consumption rate. Fast consumption patterns used in natural drinking settings, like shots and bombs, may promote acute tolerance and a greater degree of diminishing effects. For this reason, to reduce total consumption, guidelines should recommend slow consumption to reduce acute tolerance and maximize effect.

There are three areas that research into acute behavioral tolerance should now focus. First, investigations of acute tolerance should be done with an aim to increase consistency in research designs. The methodological heterogeneity of studies limits what conclusions can be drawn from comparisons between them. Those measures that reliably show acute tolerance could be used to test the effects of variables of likely consequence, such as dose, consumption time, and the effect on subsequent doses, if comparable methods are used. Second, our understanding of acute behavioral tolerance would benefit from examination with novel measures to further delineate the domains of behavior that show the effect and those that do not. The mechanism responsible for acute tolerance has not yet been identified (see Treistman and Seale [2014] for a review), and examination of acute tolerance using behavioral measures associated with specific neural structures could contribute to our understanding of the mechanism. Finally, given that both nicotine and caffeine have been suggested to affect acute behavioral tolerance (Peacock et al., 2015; Piasecki, Wood, Shiffman, Sher, & Heath, 2012; Ralevski et al., 2012), combined psychopharmacology research is warranted. The popularity of these substances with alcohol makes the combined effects on acute behavioral tolerance worthy of investigation.

References

Agarwal, D. P., & Goedde, H. W. (2012). *Alcohol metabolism, alcohol intolerance, and alcoholism: Biochemical and pharmacogenetic approaches*. Berlin, Germany: Springer Science & Business Media.

Amlung, M. T., Morris, D. H., & McCarthy, D. M. (2014). Effects of acute alcohol tolerance on perceptions of danger and willingness to drive after drinking. *Psychopharmacology, 231,* 4271–4279. http://dx.doi.org/10.1007/s00213-014-3579-1

Aston, E. R., & Liguori, A. (2013). Self-estimation of blood alcohol concentration: A review. *Addictive Behaviors, 38,* 1944–1951. http://dx.doi.org/10.1016/j.addbeh.2012.12.017

Banks, W. P., Vogler, R. E., & Weissbach, T. A. (1979). Adaptation of ethanol intoxication. *Bulletin of the Psychonomic Society, 14,* 319–322. http://dx.doi.org/10.3758/BF03329466

Baum-Baicker, C. (1985). The psychological benefits of moderate alcohol consumption: A review of the literature. *Drug and Alcohol Dependence, 15,* 305–322. http://dx.doi.org/10.1016/0376-8716 (85)90008-0

Beirness, D., & Vogel-Sprott, M. (1984). The development of alcohol tolerance: Acute recovery as a predictor. *Psychopharmacology, 84,* 398–401. http://dx.doi.org/10.1007/BF00555220

Bennett, R. H., Cherek, D. R., & Spiga, R. (1993). Acute and chronic alcohol tolerance in humans: Effects of dose and consecutive days of exposure. *Alcoholism, Clinical and Experimental Research, 17,* 740–745. http://dx.doi.org/10.1111/j.1530-0277.1993.tb00832.x

Benton, R. P., Banks, W. P., & Vogler, R. E. (1982). Carryover of tolerance to alcohol in moderate drinkers. *Journal of Studies on Alcohol, 43,* 1137–1148. http://dx.doi.org/10.15288/jsa.1982.43.1137

Bidwell, L. C., MacKillop, J., Murphy, J. G., Grenga, A., Swift, R. M., & McGeary, J. E. (2013). Biphasic effects of alcohol on delay and probability discounting. *Experimental and Clinical Psychopharmacology, 21,* 214–221. http://dx.doi.org/10.1037/a0032284

Cash, C., Peacock, A., Barrington, H., Sinnett, N., & Bruno, R. (2015).Detecting impairment: Sensitive cognitive measures of dose-related acute alcohol intoxication. *Journal of Psychopharmacology, 29,* 436–446. http://dx.doi.org/10.1177/0269881115570080

Clapp, J. D., Min, J. W., Shillington, A. M., Reed, M. B., Lange, J. E., & Holmes, M. R. (2006). Environmental and individual predictors of error in field estimates of blood alcohol concentration: A multilevel analysis. *Journal of Studies on Alcohol, 67,* 620–627. http://dx.doi.org/10.15288/ jsa.2006.67.620

Courtney, K. E., & Polich, J. (2009). Binge drinking in young adults: Data, definitions, and determinants. *Psychological Bulletin, 135,* 142 156. http://dx.doi.org/10.1037/a0014414

Cromer, J. R., Cromer, J. A., Maruff, P., & Snyder, P. J. (2010). Perception of alcohol intoxication shows acute tolerance while executive functions remain impaired. *Experimental and Clinical Psychopharmacology, 18,* 329–339. http://dx.doi.org/10.1037/a0019591

Crow, K. E., & Batt, R. D. (1989). *Human metabolism of alcohol*. Boca Raton, FL: CRC Press.

Davis, K. C., George, W. H., Norris, J., Schacht, R. L., Stoner, S. A., Hendershot, C. S., & Kajumulo, K. F. (2009). Effects of alcohol and blood alcohol concentration limb on sexual risk-taking intentions. *Journal of Studies on Alcohol and Drugs, 70,* 499–507. http://dx.doi.org/10.15288/jsad.2009.70.499

Dietler, M. (2006). Alcohol: Anthropological/archaeological perspectives. *Annual Review of Anthropology, 35,* 229–249. http://dx.doi.org/10 .1146/annurev.anthro.35.081705.123120

Dougherty, D. M., Bjork, J. M., & Bennett, R. H. (1998). Effects of alcohol on rotary pursuit performance: A gender comparison. *Psychological Record, 48,* 393–405. http://dx.doi.org/10.1007/BF03395280

Earleywine, M. (1995). Measurement Issues in the Assessment of Acute Changes in Responses to Alcohol. *Experimental and Clinical Psychopharmacology, 3,* 382–388. http://dx.doi.org/10.1037/1064-1297.3.4.382

Earleywine, M., & Erblich, J. (1996). A confirmed factor structure for the Biphasic Alcohol Effects Scale. *Experimental and Clinical Psychopharmacology, 4,* 107–113. http://dx.doi.org/10.1037/1064-1297.4.1.107

Ellinwood, E. H., Jr., Linnoila, M., Easler, M. E., & Molter, D. W. (1981). Onset of peak impairment after diazepam and after alcohol. *Clinical Pharmacology and Therapeutics, 30,* 534–538. http://dx.doi.org/10 .1038/clpt.1981.199

Erblich, J., Earleywine, M., Erblich, B., & Bovbjerg, D. H. (2003). Biphasic stimulant and sedative effects of ethanol: Are children of alcoholics really different? *Addictive Behaviors, 28,* 1129–1139. http://dx.doi.org/ 10.1016/S0306-4603(02)00221-6

Fagan, D., Tiplady, B., & Scott, D. B. (1994). Effects of ethanol on psychomotor performance under steady-state conditions. *Journal of Psychopharmacology, 8,* 75– 80. http://dx.doi.org/10.1177/026988119400800201

Ferner, R. E., Holland, M. G., Sullivan, R. W., & Dufol, A. F. (2016). The evidence for acute tolerance to human alcohol intoxication (the Mellanby effect): A systematic review. *Clinical Toxicology, 54,* 484–485.

Fillmore, M. T., Dixon, M. J., & Schweizer, T. A. (2000). Alcohol affects processing of ignored stimuli in a negative priming paradigm. *Journal of Studies on Alcohol, 61,* 571–578. http://dx.doi.org/10.15288/jsa.2000.61.571

Fillmore, M. T., Marczinski, C. A., & Bowman, A. M. (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *Journal of Studies on Alcohol, 66,* 663–672. http:// dx.doi.org/10.15288/jsa.2005.66.663

Fillmore, M. T., & Vogel-Sprott, M. (1998). Behavioral impairment under alcohol: Cognitive and pharmacokinetic factors. *Alcoholism, Clinical and Experimental Research, 22,* 1476–1482.

Fillmore, M. T., & Weafer, J. (2012). Acute tolerance to alcohol in at-risk binge drinkers. *Psychology of Addictive Behaviors, 26,* 693–702. http:// dx.doi.org/10.1037/a0026110

Gengo, F. M., Gabos, C., Straley, C., & Manning, C. (1990). The pharmacodynamics of ethanol: Effects on performance and judgment. *Journal of Clinical Pharmacology, 30,* 748–754. http://dx.doi.org/10.1002/j .1552-4604.1990.tb03638.x

Giancola, P. R. (1997). The biphasic effects of alcohol metabolism on human aggression. *Dissertation Abstracts International: B, The Sciences and Engineering, 57,* 4781.

Giancola, P. R., & Zeichner, A. (1997). The biphasic effects of alcohol on human physical aggression. *Journal of Abnormal Psychology, 106,* 598–607. http://dx.doi.org/10.1037/0021-843X.106.4.598

Ginsburg, B. C., Martinez, G., Friesenhahn, G., Javors, M., & Lamb, R. J. (2008). Acute tolerance to rate-decreasing effects of single doses of ethanol. *Physiology & Behavior, 94,* 374–383. http://dx.doi.org/10.1016/j.physbeh.2008.01.026

Grattan-Miscio, K. E., & Vogel-Sprott, M. (2005). Effects of alcohol and performance incentives on immediate working memory. *Psychopharmacology, 181,* 188–196. http://dx.doi.org/10.1007/s00213-005-22262

Hart, C. L., Ksir, C., & Ray, O. S. (2013). *Drugs, society & human behavior*. New York, NY: McGraw-Hill.

Haubenreisser, T., & Vogel-Sprott, M. (1987). Reinforcement reduces behavioural impairment under an acute dose of alcohol. *Pharmacology, Biochemistry, and Behavior, 26,* 29–33. http://dx.doi.org/10.1016/0091-3057 (87)90528-4

Hendershot, C. S., Wardell, J. D., Strang, N. M., Markovich, M. S., Claus, E. D., & Ramchandani, V. A. (2015). Application of an alcohol clamp paradigm to examine inhibitory control, subjective responses, and acute tolerance in late adolescence. *Experimental and Clinical Psychopharmacology, 23,* 147–158. http://dx.doi.org/10.1037/pha0000017

Hiltunen, A. J. (1997a). Acute alcohol tolerance in cognitive and psychomotor performance: Influence of the alcohol dose and prior alcohol experience. *Alcohol, 14,* 125–130. http://dx.doi.org/10.1016/S0741-8329 (96)00115-2

Hiltunen, A. J. (1997b). Acute alcohol tolerance in social drinkers: Changes in subjective effects dependent on the alcohol dose and prior alcohol experience. *Alcohol, 14,* 373–378. http://dx.doi.org/10.1016/ S0741-8329(96)00186-3

Hiltunen, A. J., Saxon, L., Skagerberg, S., & Borg, S. (2000). Acute tolerance during intravenous infusion of alcohol: Comparison of performance during ascending and steady state concentrations—A pilot study. *Alcohol, 22,* 69–74. http://dx.doi.org/10.1016/S0741 8329(00)00107-5

Holland, M. G., & Ferner, R. E. (2017). A systematic review of the evidence for acute tolerance to alcohol—the "Mellanby effect." *Clinical*

Toxicology, 55, 545–556. http://dx.doi.org/10.1080/15563650.2017.1296576

Irwin, C., Iudakhina, E., Desbrow, B., & McCartney, D. (2017). Effects of acute alcohol consumption on measures of simulated driving: A systematic review and meta-analysis. *Accident: Analysis and Prevention, 102,* 248–266. http://dx.doi.org/10.1016/j.aap.2017.03.001

Jellinek, E. M., & McFarland, R. A. (1940). Analysis of psychological experiments on the effects of alcohol. *Quarterly Journal of Studies on Alcohol, 1,* 272–371.

Jones, B. M. (1973). Memory impairment on the ascending and descending limbs of the blood alcohol curve. *Journal of Abnormal Psychology, 82,* 24–32. http://dx.doi.org/10.1037/h0034872

Jones, B. M., & Vega, A. (1972). Cognitive performance measured on the ascending and descending limb of the blood alcohol curve. *Psychopharmacology, 23,* 99–114. http://dx.doi.org/10.1007/BF00401185

Jones, B. M., & Vega, A. (1973). Fast and slow drinkers. Blood alcohol variables and cognitive performance. *Quarterly Journal of Studies on Alcohol, 34,* 797–806.

Kalant, H. (1971). Absorption, diffusion, distribution, and elimination of ethanol: Effects on biological membranes. In B. Kissin & H. Begleiter (Eds.), *The biology of alcoholism* (pp. 1–62). Boston, MA: Springer. http://dx.doi.org/10.1007/978-1-4615-6525-31

Kalant, H. (1996). Current state of knowledge about the mechanisms of alcohol tolerance. *Addiction Biology, 1,* 133–141. http://dx.doi.org/10.1080/1355621961000124756

Kaplan, H. L., Sellers, E. M., Hamilton, C., Naranjo, C. A., & Dorian, P. (1985). Is there acute tolerance to alcohol at steady state? *Journal of Studies on Alcohol, 46,* 253–256. http://dx.doi.org/10.15288/jsa.1985.46.253

King, A. C., de Wit, H., McNamara, P. J., & Cao, D. (2011). Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Archives of General Psychiatry, 68,* 389–399. http://dx.doi.org/10.1001/archgenpsychiatry.2011.26

Koelega, H. S. (1995). Alcohol and vigilance performance: A review. *Psychopharmacology, 118,* 233–249. http://dx.doi.org/10.1007/ BF02245951 Kosobud, A. E., Wetherill, L., Plawecki, M. H., Kareken, D. A., Liang, T., Nurnberger, J. L., . . . O'Connor, S. J. (2015). Adaptation of subjective responses to alcohol is affected by an interaction of GABRA2 genotype and recent drinking. *Alcoholism, Clinical and Experimental Research, 39,* 1148–1157. http://dx.doi.org/10.1111/acer.12749

Lahti, R. A., Pitkäniemi, J., Jones, A. W., Sajantila, A., Poikolainen, K., & Vuori, E. (2014). Cause and manner of death and phase of the blood alcohol curve. *Forensic Science International, 244,* 306–312. http://dx.doi.org/10.1016/j.forsciint.2014.09.015

LeBlanc, A. E., Kalant, H., & Gibbins, R. J. (1975). Acute tolerance to ethanol in the rat. *Psychopharmacology, 41,* 43–46. http://dx.doi.org/10.1007/BF00421304

Levine, B., & Smialek, J. E. (2000). Status of alcohol absorption in drinking drivers killed in traffic accidents. *Journal of Forensic Sciences, 45,* 3–6. http://dx.doi.org/10.1520/JFS14632J

Lipscomb, T. R., & Nathan, P. E. (1980). Blood alcohol level discrimination. The effects of family history of alcoholism, drinking pattern, and tolerance. *Archives of General Psychiatry, 37,* 571–576. http://dx.doi.org/10.1001/archpsyc.1980.01780180085010

Lukas, S., Mendelson, J., & Benedikt, R. (1986). Instrumental analysis of ethanol-induced intoxication in human males. *Psychopharmacology, 89,* 8–13. http://dx.doi.org/10.1007/BF00175181

Marczinski, C. A., & Fillmore, M. T. (2009). Acute alcohol tolerance on subjective intoxication and simulated driving performance in binge drinkers. *Psychology of Addictive Behaviors, 23,* 238–247. http://dx.doi.org/10.1037/a0014633

Martin, C. S., Balaban, C. D., & McBurney, D. H. (2006). Tonic and phasic processes in the acute effects of alcohol. *Experimental and Clinical Psychopharmacology, 14,* 209 –218. http://dx.doi.org/10.1037/1064- 1297.14.2.209

Martin, C. S., & Earleywine, M. (1990). Ascending and descending rates of change in blood alcohol concentrations and subjective intoxication ratings. *Journal of Substance Abuse, 2,* 345–352. http://dx.doi.org/10 .1016/S0899-3289(10)80006-9

Martin, C. S., Earleywine, M., Musty, R. E., Perrine, M. W., & Swift, R. M. (1993). Development and validation of the Biphasic Alcohol Effects Scale. *Alcoholism, Clinical and Experimental Research, 17,* 140–146. http://dx.doi.org/10.1111/j.1530-0277.1993.tb00739.x

Martin, C. S., & Moss, H. B. (1993). Measurement of acute tolerance to alcohol in human subjects. *Alcoholism, Clinical and Experimental Research, 17,* 211–216. http://dx.doi.org/10.1111/j.1530-0277.1993.tb00751.x

Martin, C. S., Rose, R. J., & Obremski, K. M. (1991). Estimation of blood alcohol concentrations in young male drinkers. *Alcoholism, Clinical and Experimental Research, 15,* 494–499. http://dx.doi.org/10.1111/j.1530-0277.1991.tb00549.x

Measham, F. (2006). The new policy mix: Alcohol, harm minimisation, and determined drunkenness in contemporary society. *International Journal on Drug Policy, 17,* 258 –268. http://dx.doi.org/10.1016/j.drugpo.2006.02.013

Mellanby, E. (1919). *Alcohol: Its absorption into and disappearance from the blood under different conditions* (Special Report Series No.31). London, England: Medical Research Committee.

Miller, M. A., & Fillmore, M. T. (2014). Protracted impairment of impulse control under an acute dose of alcohol: A time-course analysis. *Addictive Behaviors, 39,* 1589–1596. http://dx.doi.org/10.1016/j.addbeh.2013.10.035

Morris, D. H., Treloar, H. R., Niculete, M. E., & McCarthy, D. M. (2014). Perceived danger while intoxicated uniquely contributes to driving after drinking. *Alcoholism, Clinical and Experimental Research, 38,* 521–528. http://dx.doi.org/10.1111/acer.12252

Morzorati, S. L., Ramchandani, V. A., Flury, L., Li, T. K., & O'Connor, S. (2002). Self-reported subjective perception of intoxication reflects family history of alcoholism when breath alcohol levels are constant. *Alcoholism, Clinical and Experimental Research, 26,* 1299–1306. http://dx.doi.org/10.1111/j.1530-0277.2002.tb02670.x

Moskowitz, H., & Burns, M. (1976). Effects of rate of drinking on human performance. *Journal of Studies on Alcohol, 37,* 598–605. http://dx.doi.org/10.15288/jsa.1976.37.598

Müller, C. P., & Schumann, G. (2011). Drugs as instruments: A new framework for non-addictive psychoactive drug use. *Behavioral and Brain Sciences, 34,* 293–310.

Nicholson, M. E., Wang, M., Airhihenbuwa, C. O., Mahoney, B. S., Christina, R., & Maney, D. W. (1992). Variability in behavioral impairment involved in the rising and falling BAC curve. *Journal of Studies on Alcohol, 53,* 349–356. http://dx.doi.org/10.15288/jsa.1992.53.349

O'Connor, S., Morzorati, S., Christian, J., & Li, T. K. (1998). Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. *Alcoholism, Clinical and Experimental Research, 22,* 202–210. http://dx.doi.org/10.1111/j.1530-0277.1998.tb03639.x

Oei, T. P., & Morawska, A. (2004). A cognitive model of binge drinking: The influence of alcohol expectancies and drinking refusal self-efficacy. *Addictive Behaviors, 29,* 159–179. http://dx.doi.org/10.1016/S0306-4603 (03)00076-5

O'Malley, S. S., & Maisto, S. A. (1984). Factors affecting the perception of intoxication: Dose, tolerance, and setting. *Addictive Behaviors, 9,*111–120. http://dx.doi.org/10.1016/0306-4603 (84)90049-2

Ostling, E. W., & Fillmore, M. T. (2010). Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior. *Psychopharmacology, 212,* 465–473. http://dx.doi.org/10.1007/s00213-010-1972-y

Peacock, A., Cash, C., & Bruno, R. (2015). Cognitive impairment following consumption of alcohol with and without energy drinks. *Alcoholism, Clinical and Experimental Research, 39,* 733–742. http://dx.doi.org/10.1111/acer.12680

Peele, S., & Brodsky, A. (2000). Exploring psychological benefits associated with moderate alcohol use: A necessary corrective to assessments of drinking outcomes? *Drug and Alcohol Dependence, 60,* 221–247. http://dx.doi.org/10.1016/S0376-8716 (00)00112-5

Peterson, J. B., Rothfleisch, J., Zelazo, P. D., & Pihl, R. O. (1990). Acute alcohol intoxication and cognitive functioning. *Journal of Studies on Alcohol, 51,* 114–122. http://dx.doi.org/10.15288/jsa.1990.51.114

Piasecki, T. M., Wood, P. K., Shiffman, S., Sher, K. J., & Heath, A. C. (2012). Responses to alcohol and cigarette use during ecologically assessed drinking episodes. *Psychopharmacology, 223,* 331–344.

Pietrzykowski, A. Z., & Treistman, S. N. (2008). The molecular basis of tolerance. *Alcohol Research & Health, 31,* 298–309.

Pihl, R. O., Paylan, S. S., Gentes-Hawn, A., & Hoaken, P. N. (2003). Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcoholism, Clinical and Experimental Research, 27,* 773–779. http://dx.doi.org/10.1097/01.ALC.0000065434.92204.A1

Pishkin, V., Lawrence, B. E., & Bourne, L. E., Jr. (1983). Cognitive and electrophysiological parameters during ascending and descending limbs of the blood alcohol curve. *Alcoholism, Clinical and Experimental Research, 7,* 76 – 82. http://dx.doi.org/10.1111/j.1530-0277.1983.tb05415.x

Pohorecky, L. (1978). Biphasic action of ethanol. *Biobehavioral Reviews, 1,* 231–240. http://dx.doi.org/10.1016/0147-7552 (77)90025-0

Pohorecky, L. A., & Brick, J. (1988). Pharmacology of ethanol. *Pharmacology & Therapeutics, 36,* 335–427. http://dx.doi.org/10.1016/0163-7258 (88)90109-X

Posey, D., & Mozayani, A. (2007). The estimation of blood alcohol concentration: Widmark revisited. *Forensic Science, Medicine, and Pathology, 3,* 33–39.

Post, R. B., Tavano, L. A., & Maddock, R. J. (1998). Role of feedback in formation of acute tolerance to alcohol. *Journal of Studies on Alcohol, 59,* 723–730. http://dx.doi.org/10.15288/jsa.1998.59.723

Radlow, R. (1994). A quantitative theory of acute tolerance to alcohol. *Psychopharmacology, 114,* 1–8. http://dx.doi.org/10.1007/BF02245438

Radlow, R., & Hurst, P. M. (1985). Temporal relations between blood alcohol concentration and alcohol effect: An experiment with human subjects. *Psychopharmacology, 85,* 260–266. http://dx.doi.org/10.1007/BF00428184

Ralevski, E., Perry, E. B., Jr., D'Souza, D., Bufis, V., Elander, J., Limoncelli, D. Petrakis, I. (2012). Preliminary findings on the interactive effects of IV ethanol and IV nicotine on human behavior and cognition: A laboratory study. *Nicotine & Tobacco Research, 14,* 596–606.

Rigter, H., & Crabbe, J. C. (1980). *Alcohol tolerance and dependence*. Amsterdam, the Netherlands/New York, NY: Elsevier/North-Holland Biomedical Press, sole distributors for the U.S.A. and Canada, Elsevier/ North-Holland.

Rueger, S. Y., McNamara, P. J., & King, A. C. (2009). Expanding the utility of the Biphasic Alcohol Effects Scale (BAES) and initial psychometric support for the Brief-BAES (B-BAES). *Alcoholism, Clinical and Experimental Research, 33,* 916–924. http://dx.doi.org/10.1111/j.1530-0277.2009.00914.x

Savoie, T. M., Emory, E. K., & Moody-Thomas, S. (1988). Acute alcohol intoxication in socially drinking female and male offspring of alcoholic fathers. *Journal of Studies on Alcohol, 49,* 430–435. http://dx.doi.org/10.15288/jsa.1988.49.430

Sayed, B. A., & French, M. T. (2016). To your health! Re-examining the health benefits of moderate alcohol use. *Social Science & Medicine, 167,* 20–28. http://dx.doi.org/10.1016/j.socscimed.2016.08.034

Schuckit, M. A. (1984). Subjective responses to alcohol in sons of alcoholics and control subjects. *Archives of General Psychiatry, 41,* 879– 884. http://dx.doi.org/10.1001/archpsyc.1984.01790200061008

Schweizer, T. A., Jolicoeur, P., Vogel-Sprott, M., & Dixon, M. J. (2004). Fast, but error-prone, responses during acute alcohol intoxication: Effects of stimulus-response mapping complexity. *Alcoholism, Clinical and Experimental Research, 28,* 643–649. http://dx.doi.org/10.1097/01.ALC.0000121652.84754.30

Schweizer, T. A., & Vogel-Sprott, M. (2008). Alcohol-impaired speed and accuracy of cognitive functions: A review of acute tolerance and recovery of cognitive performance. *Experimental and Clinical Psychopharmacology, 16,* 240–250. http://dx.doi.org/10.1037/1064-1297.16.3.240

Schweizer, T. A., Vogel-Sprott, M., Danckert, J., Roy, E. A., Skakum, A., & Broderick, C. E. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacology, 31,* 1301–1309. http://dx.doi.org/10.1038/sj.npp.1300941

Söderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology, 182,* 305–317. http://dx.doi.org/10.1007/s00213-005-0096-2

Starkey, N. J., & Charlton, S. G. (2014). The effects of moderate alcohol concentrations on driving and cognitive performance during ascending and descending blood alcohol concentrations. *Human Psychopharmacology, 29,* 370–383. http://dx.doi.org/10.1002/hup.2415

Streufert, S., Pogash, R. M., Roache, J., Gingrich, D., Landis, R., Severs, W., . . . Kantner, A. (1992). Effects of alcohol intoxication on risk taking, strategy, and error rate in visuomotor performance. *Journal of Applied Psychology, 77,* 515–524. http://dx.doi.org/10.1037/0021-9010.77.4.515

Tabakoff, B., Melchior, C. L., & Hoffman, P. L. (1982). Commentary on ethanol tolerance. *Alcoholism, Clinical and Experimental Research, 6,* 252–259. http://dx.doi.org/10.1111/j.1530-0277.1982.tb04971.x

Treistman, S. N., & Martin, G. E. (2009). BK Channels: Mediators and models for alcohol tolerance. *Trends in Neurosciences, 32,* 629–637. http://dx.doi.org/10.1016/j.tins.2009.08.001

Treistman, S. N., & Seale, G. E. (2014). Molecular mechanisms underlying the development of functional and behavioral tolerance to alcohol. In A. B. C. Noronha, C. Cui, R. A. Harris, & J. C. Crabbe (Eds.), *Neurobiology of alcohol dependence* (pp. 321–346). San Diego, CA: Academic Press. http://dx.doi.org/10.1016/B978-0-12-405941-2.00016-X

Tupler, L. A., Hege, S., & Ellinwood, E. H., Jr. (1995). Alcohol pharmacodynamics in young-elderly adults contrasted with young and middle aged subjects. *Psychopharmacology, 118,* 460–470. http://dx.doi.org/10.1007/BF02245947

Viken, R. J., Rose, R. J., Morzorati, S. L., Christian, J. C., & Li, T.-K. (2003). Subjective intoxication in response to alcohol challenge: Heritability and covariation with personality, breath alcohol level, and drinking history. *Alcoholism, Clinical and Experimental Research, 27,* 795–803. http://dx.doi.org/10.1097/01.ALC.0000067974.41160.95

Vogel-Sprott, M., & Chipperfield, B. (1987). Family history of problem drinking among young male social drinkers: Behavioral effects of alcohol. *Journal of Studies on Alcohol, 48,* 430–436. http://dx.doi.org/10.15288/jsa.1987.48.430

Vogel-Sprott, M., & Fillmore, M. T. (1993). Impairment and recovery under repeated doses of alcohol: Effects of response-outcomes. *Pharmacology, Biochemistry, and Behavior, 45,* 59–63. http://dx.doi.org/10.1016/0091-3057 (93)90086-9

Vogel-Sprott, M., & Sdao-Jarvie, K. (1989). Learning alcohol tolerance: The contribution of response expectancies. *Psychopharmacology, 98,* 289–296. http://dx.doi.org/10.1007/BF00451677

Wang, M. Q., Nicholson, M. E., Mahoney, B. S., Li, Y., & Perko, M. A. (1993). Proprioceptive responses under rising and falling BACs: A test of the Mellanby effect. *Perceptual and Motor Skills, 77,* 83–88. http://dx.doi.org/10.2466/pms.1993.77.1.83

Watson, P. E., Watson, I. D., & Batt, R. D. (1981). Prediction of blood alcohol concentrations in human subjects. Updating the Widmark Equation. *Journal of Studies on Alcohol, 42,* 547–556. http://dx.doi.org/10.15288/jsa.1981.42.547

Weafer, J., & Fillmore, M. T. (2012). Acute tolerance to alcohol impairment of behavioral and cognitive mechanisms related to driving: Drinking and driving on the descending limb. *Psychopharmacology, 220,* 697–706. http://dx.doi.org/10.1007/s00213-011-2519-6

Wellman, R. J., Contreras, G. A., Dugas, E. N., O'Loughlin, E. K., & O'Loughlin, J. L. (2014). Determinants of sustained binge drinking in young adults. *Alcoholism, Clinical and Experimental Research, 38,* 1409–1415. http://dx.doi.org/10.1111/acer.12365

Wiers, R. W., & Kummeling, R. H. (2004). An experimental test of an alcohol expectancy challenge in mixed gender groups of young heavy drinkers. *Addictive Behaviors, 29,* 215–220. http://dx.doi.org/10.1016/S0306-4603 (03)00081-9

Wilson, J. R., Erwin, V. G., & McClearn, G. E. (1984). Effects of ethanol: I. Acute metabolic tolerance and ethnic differences. *Alcoholism, Clinical and Experimental Research, 8,* 226–232. http://dx.doi.org/10.1111/j.1530-0277.1984.tb05682.x

Chapter 3: Experimental Studies

3.1 Explanatory Statement

Our review identified potential areas of research that could be addressed in this thesis. Despite a large number of prior studies reporting acute tolerance, there was still a clear gap in our understanding of which objective measures show the effect. The most straightforward way to address this was to test for the effect with objective behavioural measures. The difference between speed and accuracy in cognitive tasks showing acute tolerance was a common theme in literature, and provided a rationale for investigating the effect in Response Inhibition and Information Processing with measures that were either novel or worthy of repeated study.

The Mellanby paradigm was an obvious choice for the experimental design to use in our investigations. It is a widely accepted design that is simple and easy to administer. As discussed in the review the Mellanby paradigm has some limitations. However, it was decided to be the most suitable method for the scope of our investigation. It was noticed during the review that very few studies have examined acute tolerance using more than one paradigm. Some paradigms are inherently incompatible like the Mellanby and steady-state, which use differently shaped BAC curves. However, data collected throughout the time course of the dose at multiple times can be examined in numerous different ways to show a decrease in dose effect. As mentioned in the review, there has been a lack of uniformity in studies using the Mellanby paradigm, but there has also been a lack of explanation and rationale for how the paradigm is used to provide evidence of an acute tolerance effect. For this reason, we explicitly stated the criteria we would use to determine if an acute tolerance effect could be reported from data from the Mellanby paradigm. In addition to the commonly used criteria of an observed decrease in the effect of alcohol within the alcohol group, we also included the criterion of a statistically significant interaction between the dose and placebo group, as a means of protecting against type-1 error.

The reliability of finding acute tolerance to subjective intoxication highlighted in the review suggested that it could be used as a kind of litmus test when researching the effect in objective

measures. If acute tolerance was absent in measures of subjective intoxication it could suggest that conditions of the experiment were not appropriate for testing the effect. While on the other hand, a finding of acute tolerance in subjective intoxication when the effect is absent in objective measures would lend support to the theory that the domain does not show the effect, as the conditions were appropriate to produce the effect in another domain. Subjective ratings are also not susceptible to practice effects in the same way that objective measures are and can be very quickly and easily administered (Gift, 1989). All of which means that subjective measures can be taken at many points during the dose to provide data for paradigms that require a larger volume of data.

A final finding in the review that motivated further study was that no definitive conclusions could be drawn about the influence of dose size on acute tolerance. The lack of uniformity in the methods and findings of past studies testing the effect of dose-size meant that the effect of dose-size required further study. This provided another avenue of investigation for this current research, which we pursued in the second study.

To address these issues, we designed two experimental studies. In the first study, measures of visual information processing speed, response inhibition and subjective intoxication were compared between the limbs of the BAC curve at approximately .05%, after participants were given a medium[14] dose of alcohol, or a placebo. Participants who received a placebo were tested at equivalent times to when dosed participants were tested (post-dose). The results are reported in 3.2. The second study also used the Mellanby paradigm to examine the effect with measures of response inhibition, executive processing decision-making speed and subjective intoxication. Measures were again compared at a BAC of approx. .05%, but in this study participants were given a placebo or either a small or large size dose. The results are reported in 3.3. Because measures of subjective intoxication and BAC were taken at multiple times throughout the dose, paradigms aside from Mellanby's could be used to test the data for acute tolerance. An additional analysis of the data from this study with the peak comparison and rate of recovery paradigm was conducted and reported in 3.4.

[14] Small, Medium and Large in this case referring to the three sizes tested in this thesis.

Cash, Peacock, Barrington, Sinnett, and Bruno (2015) was one of the studies reviewed that used a cumulative dose protocol and did not find an acute tolerance effect. In contrast to those studies that aimed to test for changes in the dose-effect, Cash et al. (2015) tested the stability and sensitivity of alcohol impairment throughout the dose for several cognitive measures, one being the *Inspection Time Task* (ITT). As no substantial change in impairment of ITT performance was found, the authors concluded that "The ITT is sensitive to alcohol-induced impairment at 0.050% BrAC, the legal limit for driving in several countries, both when BAC is increasing and when BAC is decreasing" (Cash et al., 2015). The ITT is a valid measure of information processing which had reliably shown an effect of alcohol in previous studies under doses that were practical (and ethical) to administer (Dry et al. 2012). It was also easy to access and administer with the hardware we had available. The ITT was used in the first study to replicate the Cash et al. (2015) study with a modified dose protocol, giving a single bolus administration more commonly used in studies which do find acute tolerance. We also extended the replication to include the Sustained Attention to Response Task (SART). The SART was among the cognitive performance measures examined in Dry et al. (2012) that showed a significant dose-response effect from alcohol. The SART is also a unique measure of response inhibition, different to those that had found the pattern of effect between speed and accuracy. It was included as a novel test for acute tolerance to further examine the effect in response inhibition.

The Stop-Signal-Paradigm is another unique measure of response inhibition distinct from those previously used to examine acute tolerance that we included as another novel measure of the effect in response inhibition in the second study. The Multiple Choice Reaction Time task (MCRT) was chosen as a second cognitive measure to be used in the second study. It had previously shown acute tolerance at similar BAC's to those we would be testing (Miller & Fillmore, 2014), and was expected to be a measure that would allow for an examination of the effect of dose-size. To produce an adequate difference in the peak BAC between the different size doses, while still being able to test at equivalent BACs on both limbs, a dose slightly lower than that used in the first study was used as the small dose. The large dose was selected to be only slightly higher than that in the first study to prevent the negative effects of higher BACs and rapid consumption.

Visual Analogue Scales (VAS) are often used in research to measure subjective phenomena (Gift, 1989). Our review found that they were the most commonly used measure to show acute tolerance. The wording of the anchoring at each end of the scale differed very slightly between studies[15]. Some also used multiple scales for different dimensions of the subjective effect of alcohol, that is, sedation, arousal, tiredness, high. As these all fall under the overarching concept of "feelings of intoxication", we used only one scale labelled "current feeling of intoxication". Anchors were from "not at all" to "very much" following the modal practice of past studies. Because the VAS proved practical in the first study it was kept as the measure of subjective intoxication in the second study. Because of its simplicity, it can be administered quickly enough to measure subjective intoxication repeatedly throughout the dose, and was thus able to gather the quantity of data needed for examination with other paradigms.

The fourth manuscript was largely motivated by a previous study by Martin and Moss (1993) which, to our knowledge, is the only other study to examine acute tolerance to subjective intoxication using multiple paradigms. Martin and Moss calculated acute tolerance scores for each participant from three different paradigms. They concluded that under a dose of 0.8g/kg, 80% of subjects showed acute tolerance with the Mellanby paradigm, 85% with the area under the curve, and 95% with the rate of recovery. We aimed to follow this example of comparing examinations of acute tolerance across multiple paradigms to test whether findings are consistent between paradigms for the same data using analyses of group scores.

[15] For example, not drunk at all to most drunk I've ever been, etc. etc.

Statement of Authorship

Title of Paper	Acute tolerance to alcohol-induced impairment in cognitive performance
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Comley, R. E., & Dry, M. J. (2020). Acute tolerance to alcohol-induced impairment in cognitive performance. *Experimental and Clinical Psychopharmacology*.

Principal Author

Name of Principal Author (Candidate)	Ross Edward Comley		
Contribution to the Paper	Experimental design, data collection, analysis, and interpretation, drafting of manuscript		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19/10/2020

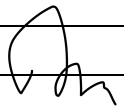
Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Matthew Dry		
Contribution to the Paper	General guidance as supervisor		
Signature		Date	20-10-20

3.2 Manuscript: Acute tolerance to alcohol-induced impairment in cognitive performance

Acute Tolerance to Alcohol-Induced Impairment in Cognitive Performance

R. Edward Comley

Matthew J. Dry

Abstract

Acute tolerance is a rapid decrease in the effect of alcohol relative to the blood alcohol concentration (BAC) occurring within the duration of a single dose of alcohol. It remains uncertain which cognitive domains are susceptible to acute tolerance, because findings vary between tasks used to measure the effect of alcohol. This study examined acute tolerance in subjective intoxication and in two cognitive domains: information processing, measured using the Inspection Time Task (ITT), and response inhibition, measured with the Sustained Attention to Response Task (SART). Forty participants were allocated to either an alcohol or placebo group. After baseline measures, the alcohol group were given an active dose to produce a peak BAC of 0.07%, whereas the placebo group received a placebo beverage. ITT and SART performance were measured at a BAC of 0.05% twice during the course of the dose, once when BAC was ascending and again when descending. The placebo group was tested at equivalent times. When BAC was ascending, the alcohol group showed increased ratings of subjective intoxication and impaired performance on the ITT. Consistent with an acute tolerance effect, ratings of subjective intoxication and impairment on the ITT in the alcohol group were lower when BAC was descending. Performance on the SART was not found to be affected by alcohol. The findings suggest information processing is a domain of behavior that shows acute tolerance to alcohol and that the subjective intoxication felt at a BAC of 0.05% can decrease substantially within the duration of a single dose.

Public Health Significance Statement

This study found that the effect of alcohol on visual information processing speed and subjective intoxication at a blood alcohol concentration of 0.05% decreased within the duration of a single dose. Guidance for responsible drinking and future research into the effects of alcohol should consider both the demonstrated decrease in the effect of alcohol and the observed variance in effect between behavioral domains. If changes in the dose-effect were accounted for, estimates of the effects of alcohol could be more accurate and consumers' decisions regarding consumption could be better informed.

Keywords: alcohol, acute tolerance, Mellanby effect, response inhibition, information processing

Introduction

The psychoactive effects that alcohol (ethanol) produces at certain doses are a primary reason for people consuming it. When consumed, alcohol acts as a general central nervous system depressant, which can be of benefit to certain behaviors (social interaction, coping with psychological stress; Müller & Schumann, 2011; Vengeliene, Bilbao, Molander, & Spanagel, 2008). Conversely, alcohol also causes impairment in an array of behavioral domains. It has been reliably demonstrated to affect performance in cognitive tasks (Dry, Burns, Nettelbeck, Farquharson, & White, 2012), and this cognitive impairment has been implicated as a potential contributor to some of the negative outcomes of alcohol consumption, such as road accidents involving drunk drivers (Calhoun, Pekar, & Pearlson, 2004; Weissenborn & Duka, 2003).

The impairment to cognitive abilities caused by alcohol is generally dose-dependent, meaning that the magnitude of the effect increases with the size of the dose (Hart, Ksir, & Ray, 2013; Pohorecky &Brick, 1988). It is interesting, however, that variance in the magnitude of the drug's effect relative to the size of the dose (*dose effect*) is also often observed (Fillmore & Vogel-Sprott, 1998). For a given individual, doses of equal size can produce differing levels of impairment across different situations. The degree of impairment that alcohol causes is often estimated based on the size of the dose alone, but estimates of the effects of alcohol could be made more accurate if changes in the dose effect were accounted for.

Tolerance is a decrease in dose effect. When it occurs, the magnitude of the effects produced by a dose of alcohol diminishes and a larger dose becomes required to elicit the same degree of impairment as prior to the onset of tolerance (Vogel-Sprott &Sdao-Jarvie, 1989). Tolerance can be categorized by the timeframe over which it is observed. The focus of this article is *acute tolerance,* which is a rapid decrease in dose effect that develops within the duration of a single dose (Sullivan & Pfefferbaum, 2014). This can be contrasted with *chronic tolerance,* which is seen on a longer time scale when the relative effect produced by a dose of a given size is observed to be less after accumulative doses.

The unit of measure for the size of a dose, at a given time point within its duration, is the blood alcohol concentration (BAC). A decrease in dose effect consistent with acute tolerance can be observed during a dose by examining the relative changes in drug effect while controlling for changes in BAC (Rigter & Crabbe, 1980). In past studies, the most common way of controlling for changes in BAC has been to directly compare the drug effect between two time points during a dose when BAC is

equivalent. This is achieved by taking measures on each "limb" of the BAC curve: once when the BAC is ascending to peak and again when the BAC is descending (Crow & Batt, 1989; Holland & Ferner, 2017). If acute tolerance occurs, the observed effect of alcohol is greater on the ascending limb of the BAC curve and less on the descending limb (at equivalent BACs). This was the method used by Mellanby, who first reported an acute tolerance effect in 1919 (Mellanby, 1919). Even though acute tolerance has repeatedly been researched over the last 100 years, there is still uncertainty as to which aspects of behavior effected by alcohol show the effect.

This study used the Mellanby paradigm to test for acute tolerance in two cognitive domains. Acute tolerance does not seem to develop uniformly across different domains of behavior, because findings vary depending on the task employed to measure the effect of alcohol (Ginsburg, Martinez, Friesenhahn, Javors, & Lamb, 2008; Schweizer & Vogel-Sprott, 2008). Some behavioral measures have shown acute tolerance more reliably than have others, but it remains unclear which domains of behavior show the effect despite its having been demonstrated in numerous measures (for a review, see Comley & Dry, 2019). This study aimed to contribute to resolving this uncertainty by examining the effect in two distinct cognitive domains: information processing and response inhibition. Acute tolerance is most reliably found in measures of the subjective effects of alcohol like "feelings of intoxication," sedation, or mood. Studies on acute tolerance that include both subjective and objective measures have often found a decreased effect of alcohol relative to the BAC for subjective ratings of intoxication, even when the dose effect for objective measures does not change (Gengo, Gabos, Straley, & Manning, 1990; Marczinski & Fillmore, 2009; Söderlund, Parker, Schwartz, & Tulving, 2005; Starkey & Charlton, 2014). This study included a measure of subjective intoxication as a reliable indicator of acute tolerance to ascertain whether the conditions tested were suitable to test for the effect in other domains.

Tasks that use both speed and accuracy as indices of cognitive performance have a tendency for measures of speed to show acute tolerance to the impairment from alcohol, whereas measures of accuracy do not (Schweizer & Vogel-Sprott, 2008). This pattern has been observed across various cognitive domains (inhibition, working memory, learning). Measures of speed in these tasks are often sensitive to individual differences in motor speed (Jensen, 2006). Therefore, attributing the acute tolerance seen in these measures to a specific cognitive domain is problematic because the influence of motor speed cannot be decoupled from the cognitive performance being measured.

Acute tolerance to alcohol-induced impairment in information processing has been previously found in studies employing tasks that used both response speed and response accuracy as measures of performance. Both Schweizer, Jolicoeur, Vogel-Sprott, and Dixon (2004) and Schweizer et al. (2006) found that alcohol impaired reaction time (RT) and accuracy of performance in separate information processing tasks. However, in both studies, a decrease in the effect of alcohol (relative to the dose) was only found for RT measures. The Inspection Time Task (ITT; Vickers, Nettelbeck, & Wilson, 1972) is a measure of visual information processing speed shown to be susceptible to impairment from moderate doses of alcohol (Dry et al., 2012) and is a unique measure of information processing in that it does not require speeded responses. The ITT measures visual information processing speed from the minimum stimulus exposure duration needed to accurately discern the direction (left vs. right) of an asymmetrical target, with no time limit for response. In the absence of speeded responses, performance in the ITT is not influenced by motor speed, making it an appropriate task for examining acute tolerance in information-processing speed specifically.

The stability of the dose effect of alcohol on ITT performance has been previously examined using the Mellanby paradigm (Cash, Peacock, Barrington, Sinnett, & Bruno, 2015; Peacock, Cash, & Bruno, 2015). Cash et al. (2015) reported that participants who had received alcohol required a stimulus exposure duration 23% longer than did a placebo group when their BAC was 0.05% on the ascending limb. However, an acute tolerance effect was not found as impairment on the task at a BAC of 0.05% was similar on both limbs. A potential reason for the absence of acute tolerance in these studies is that a "cumulative" dosing protocol was used, in which the dose was divided and administered incrementally across several time points. This resulted in the ascending limb measures being taken before the entire dose was consumed and thus being under the effect of a smaller dose. This dosing protocol is different from that used in most studies reporting the effect, which administer the entire dose before measures of the drug-effect are taken. The present study sought to test for acute tolerance on the ITT using a single dose of alcohol.

Like measures of accuracy in information processing tasks, measures of accuracy in response inhibition tasks have also shown a tendency to be resistant to acute tolerance, whereas measures of speed (RT) show the effect more often (Schweizer & Vogel-Sprott, 2008). This pattern has been found most on the cued go/no-go task (Fillmore, Marczinski, & Bowman, 2005; Fillmore & Weafer, 2012; Ostling & Fillmore, 2010). In the task, go cues produce learned motor responses that must be withheld when rare no-go stimuli are presented (Miller & Fillmore, 2014). Response inhibition is measured

using errors of commission (failures to inhibit a response) to no-go stimuli preceded by a go cue. Another response inhibition task, the Sustained Attention to Response Task (SART) also measures errors of commission to a non-target (i.e., no-go) stimulus, but inhibition failures are attributable to lapses of sustained attention (Manly, Robertson, Galloway, & Hawkins, 1999). Performance in the SART involves frequent continual key presses to repeatedly presented targets, with occasional withholding of responses to non-targets. When rare non-targets occur, active, controlled processing must be triggered to overcome the response acquired from the previously presented targets.

Both the SART and cued go/no-go task measure response inhibition using errors of commission, which are inherently dissociated from motor speed performance because successful performance depends on the absence of motor responses. Both tasks do include RT to targets as a measure of speed. However, the tasks differ in the type of response activation that must be inhibited. Activation tendencies in the cued-go/no-go task are attributable to the rapid development of responses to cues as a preparatory process for the execution of the motor response elicited by the cues. In contrast, activation tendencies in the SART are attributable to the development of automatic responses to targets as attention-undemanding, frequent stimuli. Alcohol has been demonstrated to impair performance on the SART, causing response accuracy to decrease as BAC increases. Dry et al. (2012) found significant impairment at a BAC of 0.048%. The task has yet to be used to examine acute tolerance and was included in this study to test for the effect with a novel measure of response inhibition.

Previous studies that have employed the Mellanby paradigm have not used a uniform method of testing for acute tolerance. Evidence of an effect of alcohol has been shown using both between-groups (alcohol vs. placebo control) and within-group (pre- vs. post-dose) comparisons, both of which are valid; however, between-groups comparisons are able to control for extraneous changes in a measure that occur with repeated administrations (i.e., testing effects). Studies have also differed in how data from the paradigm have been used to show a decrease in the effect of alcohol. The lack of a uniform method for testing data from the Mellanby paradigm has been an obstacle to comparing results between studies and raises doubts about the robustness of the acute tolerance effect, because data from a particular study may meet one standard of evidence but not another.

The present study tested data from the Mellanby paradigm against three criteria for acute tolerance. The first criterion was an effect of alcohol on the ascending limb, because there must be an initial effect to recover from for a decrease in dose effect to be shown. An alcohol effect was tested for

by comparing measures between a group dosed with alcohol and a placebo control group. The second criterion was that the size of the effect of alcohol on the descending limb was smaller than on the ascending limb (at an equivalent BAC). An increase in the difference would suggest an increase in the dose effect (acute sensitivity). To confirm a change in the dose effect between limbs, the third criterion was the presence of a statistically significant interaction between the limb and the group. If the three criteria were met, an analysis of the change between limbs, within groups, was conducted to examine the nature of the acute tolerance effect.

Method

Participants

This study was approved by the University of Adelaide's Human Research Ethics Committee. Forty-two first-year university students were recruited to take part in the study, and course credit was granted in return for participation. Recruitment was conducted via an online scheduling system. Each participant's eligibility to participate was subject to the following criteria: (a) ages 18–45 years, (b) not currently pregnant or lactating, (c) no major medical or psychiatric conditions, (d) no uncorrected visual disorders, (e) no dependence on any substance (excluding nicotine), (f) fluent in English, (g) no history of alcohol-related problems, (h) not taking medication having a stimulative or sedative action, (i) had consumed at least three alcoholic beverages on at least one occasion in the past month, and (j) had not consumed alcohol or other drugs (except nicotine) in the previous 24 hr.

The age range was limited to ensure that participants were of legal drinking age but unlikely to be affected in their task performance by age-related cognitive decline, which could introduce confounding variance and reduce statistical power. Criterion (i) was included to ensure that participants had some familiarity with the doses of alcohol being given. Participants were screened for risky drinking behavior using the Alcohol Use Disorders Identification Test (AUDIT). This is a 10-item questionnaire reporting the occurrence and severity of alcohol-related problems during the twelve months prior (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). Participants who scored eight or higher were excluded, because this is the recommended cut-off score for identifying risky drinking behavior (Conigrave, Hall, & Saunders, 1995), but no participant reached this criterion level. Two subjects were unable to complete the testing procedure, after becoming nauseous from the consumption of the dose. This resulted in a final sample of 40 participants (18 women) between the ages of 18 and 30 years (M = 20, SD = 3). Nineteen (47.5%) self-identified as Caucasian or White, 10

as Australian, two as Indian, two as mixed, one as Albanian, one as Chinese, one as Filipino, one as Malaysian, one as Persian, and one as Vietnamese; one gave no response.

Table 4.
Participant characteristics of each dose group

	Active-dose group (n = 20)		*Placebo group (n = 20)*	
Characteristic	*M (SD)*	*n*	*M (SD)*	*n*
Age (years)	20.3 (3.5)		19.7 (2.6)	
Gender (female)	9		9	
AUDIT score,	4.9 (2.3)		4.0 (2.3)	

Note. AUDIT = Alcohol Use Disorders Identification Test.

Measures

All cognitive tasks were programmed at the University of Adelaide and installed on Windows XP (Microsoft Corporation, Redmond, WA) machines. Tasks included onscreen instructions. Peripheral computer hardware was standardized across machines; an HP corded mouse (1,000 dpi) and keyboard were used (Hewlett-Packard, Palo Alto, CA).

ITT.

The Inspection Time task (ITT) is a computerized cognitive performance task that measures visual information processing speed from the minimum stimulus exposure duration needed to accurately make a two-alternative forced-choice discrimination. In the task, participants are presented with an asymmetrical target symbol in the center of the computer screen: a horizontal line with a vertical line (leg) hanging from each end. Participants are instructed to discern which leg of the target (left or right) is shorter and make the corresponding response with either the left or right mouse button. Prior to the presentation of a target symbol, a white cross is displayed for 500 ms as both a warning cue and a fixation point to orient participants to the location of the target on the screen. Before responses are able to be made after each target presentation, the target symbol is backward-masked by a similar symmetrical symbol (twin lightning bolts) displayed for 290 ms; this interval removes any influence of motor speed on performance. Participants are advised to take as long as they require to make a response and that the speed of responses is not important. The duration of target display before presentation of the mask is dependent on performance, following an adaptive staircase algorithm operating to measure the temporal threshold at which a participant can discriminate a difference between left and right facing targets (for details see Preiss & Burns, 2012). The duration

begins at 256 ms and either decreases by 13 ms increments after every three consecutive correct responses or increases by 13 ms after every single incorrect response. The task ends after eight reversals in direction on the staircase.

SART.

The SART is a computerized cognitive performance task that provides measures of sustained attention from response inhibition errors and response times. During the task, randomly ordered digits between 1 and 9 in various font sizes (ranging from 12 mm to 29 mm onscreen) are displayed in the center of the screen for a duration of 245 ms. Immediately following each digit display, a mask is displayed for 900 ms. The duration from digit onset to mask offset for each trial is 1,145 ms. Participants are instructed to respond (left mouse button click) to the presentation of all digits except the digit *3* (go trials) and withhold (inhibit) responses when a *3* is presented (no-go trials), giving equal import to both speed and accuracy of responses. The task comprises a total of 225 trials, of which 25 are no-go trials occurring randomly throughout the task (for details see Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Task performance is measured by the proportion of incorrect responses to no-go trials (errors of commission), the median RT in go trials (RT), and post-error slowing (the increase in RT after an error).

Subjective intoxication.

Subjective effects of alcohol were measured using a visual analogue scale (VAS) labelled *level of felt intoxication*. A 100-mm-long black line was printed on a length of paper, with each end anchored from *not at all* to *very much,* left to right. Participants were instructed to mark a vertical line at the point on the scale that equated to the magnitude of their current feelings of intoxication. Ratings were recorded as millimeters from baseline.

Breathalyzer.

BAC was measured from breath samples using a standardized breathalyzer (Lion brand Model 500P). Note that readings are reported as BAC and not breath alcohol concentration (BrAC), because the breathalyzer calculates BrAC to give readings as BAC. Participants were kept blind to the readings from the breathalyzer.

Demographics.

General demographic information for each participant was collected via a self-report questionnaire. Responses regarding gender and body weight were used to calculate alcohol doses. A digital scale was used to make a measure of participants' body weight.

Procedure

Upon registering for participation, participants were instructed to fast for the four hours prior to their session, after eating a normal breakfast. They were also instructed to refrain from consuming alcohol or other drugs (except nicotine), for 24 hr prior to their participation. Participants were randomly pre-allocated to either an active-dose or placebo-control condition. (See Table 4)

Upon arriving at the laboratory, participants were briefed on the procedure, the nature of the measures, and the effects of alcohol. After giving informed consent, participants completed the demographic questionnaire and the AUDIT. A baseline measure of BAC was taken to ensure that participants began the procedure with a BAC of 0%, and baseline ratings of subjective intoxication were recorded to familiarize participants with the VAS. Participants then completed the practice and baseline trials of the SART and ITT. Baseline scores were used to control for individual differences in performance. Active-dose and placebo-control groups did not differ significantly in baseline performance on any task ($p > .05$).

When participants were completing baseline trials, the experimenter calculated and prepared the dosed beverages. Those in the alcohol group were given alcohol in the form of vodka (37.5% alcohol/vol) mixed with orange juice in a 2:9 mix. Dose volumes for each participant in the alcohol group were calculated to produce a peak BAC of 0.07% using the Widmark equation, which calculates the volume of alcohol needed to raise an individual's BAC to a specified level based on the participant's sex and body weight. Participants in the placebo-control group received an equal volume of juice with a less than effective dose of alcohol. Participants were blind to their dose condition and told that the beverage may or may not contain alcohol. To give the impression that the placebo beverage contained a dose of alcohol, we floated 3 ml of vodka on the surface of the drink and coated on the rim of the cup. Beverages in both conditions were equally divided into three cups, and participants were instructed to consume all three beverages at an even pace over 10 min.

After the beverages were drunk, BAC measures were taken repeatedly to monitor and track the course of BAC in order to administer measures at times when had reached or were approaching the target BAC. Measures were taken a minimum of every four minutes prior to ascending limb measures, then every ten minutes after. Subjective intoxication ratings were also taken with each BAC measure. When BAC reached 0.05% participants completed the SART and ITT for the second time. Once BAC had peaked and then declined back to 0.05% participants were again tested on the SART and ITT. Each participant in the placebo-control group was anchored to a participant in the dose

group and tested at equivalent times, including breathalyzer and subjective intoxication measures. Light snacks were served to participants after the descending limb trials. Participants remained until their BAC was less than 0.01%, after which time they were debriefed and permitted to leave.

Data Analysis

Analyses were conducted using IBM SPSS Statistics 22. To keep the order of analyses consistent with the rationale of the Mellanby paradigm described in the introduction, we did not follow the orthodox practice of testing for an interaction first. Instead, analyses were ordered based on the three criteria detailed earlier. For ITT and SART performance, an effect of alcohol on the ascending limb of the BAC curve was examined by comparing scores between dose conditions using a one-way analysis of covariance (ANCOVA), treating baseline scores as a covariate. If an effect of alcohol was found on the ascending limb, an effect of alcohol on the descending limb was also tested for by comparing scores between dose conditions using one-way ANCOVA, treating baseline scores as a covariate. If the effect of alcohol on the descending limb was smaller than on the ascending limb, then an interaction between dose condition and limb was tested using a 2 (group) × 2 (limb) mixed ANCOVA, in which limb was the within-subject factor and baseline scores were treated as a covariate. If the three criteria for acute tolerance were met, the nature of the effect was examined with paired-samples *t* tests for each dose condition, using adjusted scores from the previous analyses to control for baseline differences in performance.

For subjective intoxication ratings, the requirement that BAC and intoxication be zero when testing commenced meant there was no need to control for baseline differences; accordingly, a different analysis was conducted. Group differences on each limb were tested using independent-samples *t* tests. If an effect of alcohol was found on the ascending limb, and this effect was smaller on the descending limb, then an interaction between dose condition and limb was analyzed with 2 (group) × 2 (limb) mixed analysis of variance, with limb as the within-subject factor. If the three criteria for acute tolerance were met, the nature of the effect was examined using paired-samples *t* tests for each dose condition.

Results

Blood Alcohol Concentrations

No detectable BAC was observed in baseline measures from the alcohol group or in any measure from the placebo-control group once residual mouth alcohol from the placebo beverage had

been eliminated. The analysis of BAC data was therefore restricted to that from the alcohol group, post-beverage administration. The mean peak BAC reached in the alcohol group was 0.066% (*SD* =0.008), which was lower than the target BAC of 0.07%, t (19) = -2.07, p = .052, d = 0.46. Figure 7 plots the mean group BAC and individual participant BAC levels on the ascending limb, at peak, and on the descending limb. BACs at the commencement and completion of objective tasks on each limb were averaged to yield a test-specific BAC for each limb for each participant. The mean test-specific BAC on the ascending limb was 0.052%, and on the descending limb 0.053%. The mean start time for ascending limb measures was 16 min post-beverage consumption (*SD* = 10.0 min). The mean start time for descending limb measures was 95 min post-beverage consumption (*SD* = 21.9 min). Comparison of test-specific BACs using a paired-samples t test showed differences between limbs were not statistically significant, t (19) = 0.67, p = .5, d = 0.2. Bayes factors indicated that these data were more probable under the null hypothesis than under the alternative (4.72 to 1). Thus, changes in BAC were suitably controlled to test for a decrease in the dose effect, because a reduction in the effect of alcohol from the ascending limb to the descending limb could not be attributed to a decrease in BAC.

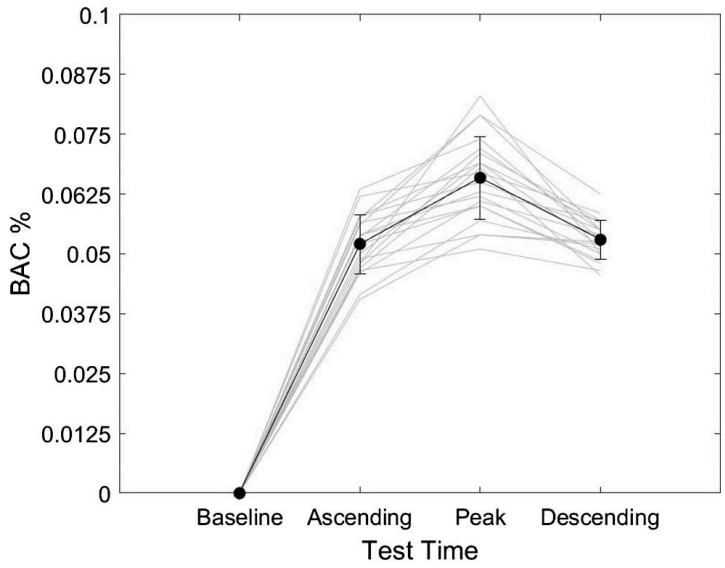


Figure 7. Means and error bars (±1 SD) for blood alcohol concentration (BAC), together with individual participant BAC levels measured at baseline, on the ascending limb, at peak BAC.

Group Differences in Alcohol Effect and Acute Tolerance

Subjective intoxication.

The mean maximum subjective intoxication ratings in the alcohol (37.05, *SD* = 22.98) and placebo (11.5, *SD* = 14.97) groups were significantly different, t (38) = 4.16, p < .001. However, the

mean time of maximum ratings (minutes post consumption) in the alcohol (33.85, *SD* = 16.56) and placebo (29.95, *SD* = 38.54) groups was not significantly different, t (38) = 0.42, p = .68. Figure 8 plots subjective ratings from each group during testing on both limbs. Although both groups gave higher ratings of subjective intoxication on the ascending limb, the alcohol group gave higher ratings during measures on each limb and showed a greater decrease between limbs. Comparison of subjective intoxication ratings between groups on each limb using independent-samples *t* tests showed an effect of alcohol. Participants in the alcohol group gave higher ratings of subjective intoxication than did the placebo-control group on the ascending limb, t (38) = 4.50, p < .001, d = 1.42. Consistent with the presence of acute tolerance, the effect of alcohol on subjective intoxication was smaller on the descending limb than on the ascending limb, t (38) = 3.43, p = .01, d = 1.09. This decrease was confirmed by a statistically Significant Group × Limb interaction, F (1, 38) = 8.71, p < .01, η^2 = .12. There was also a significant main effect of limb on ratings of subjective intoxication, F (1, 38) = 22.13, p < .001, η^2 = .32, due to an overall decrease in ratings from the ascending to descending limb. Follow-up analysis with a paired-sample *t* test within the alcohol group found that the decrease in ratings between limbs was significant, t (19) = 4.72, p < .001, and substantial (d = 0.69). But changes between limbs in the placebo group were not significant, t (19) = 1.49, p = .15.

Inspection Time Task.

Due to a technical error, ITT data from one participant were not recorded. Figure 9 plots the adjusted mean ITT score on each limb for each group and shows a pattern consistent with acute tolerance, because the alcohol group required longer stimulus displays (impairment) than did the placebo group on the ascending limb, and the size of this effect diminished between limbs, owing somewhat to performance in the alcohol group improving. Comparisons of scores between groups on each limb using one-way ANCOVA found the difference in ITT scores between the alcohol and placebo groups on the ascending limb was statistically significant, F (1, 37) = 5.81, p = .021, d = 1.02, confirming an effect of alcohol (impairment). This difference between groups was smaller on the descending limb, F (1, 37) = 0.83, p = .37, d = 0.13, consistent with a decrease in the effect of alcohol. This difference in alcohol effect between limbs was confirmed by a statistically significant Group × Limb interaction, F (1, 37) = 6.07, p = .019, η^2 = .012. The main effect of limb was not significant (p = .6). Follow-up analysis within dose conditions using paired-sample *t* tests found that the improvement in performance seen in the alcohol group between limbs was significant, t (18) = 2.18, p = .04, d = 0.68. But the decrease in performance seen in the placebo group was not, t (19) = 1.63, p = .12.

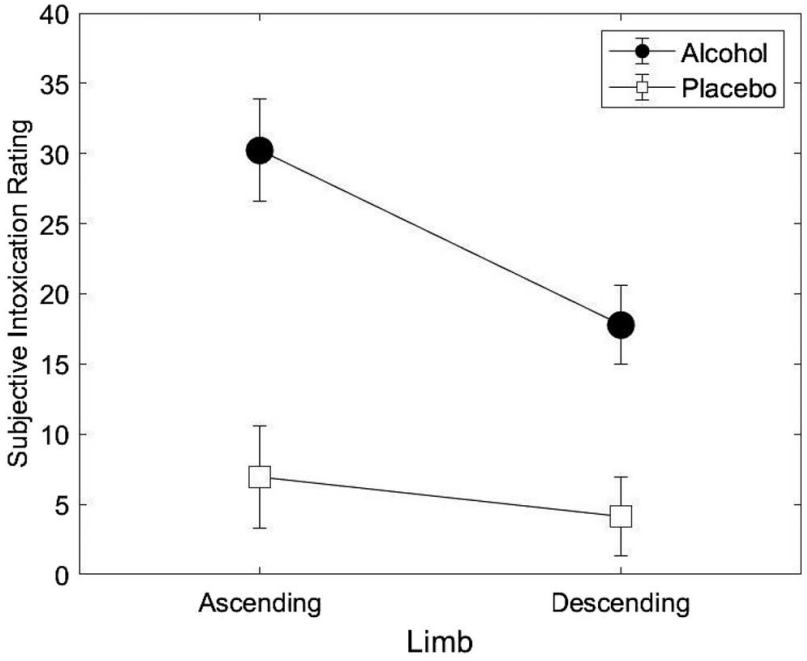


Figure 8. Mean ratings and standard errors of subjective intoxication in dose and placebo groups on each limb.

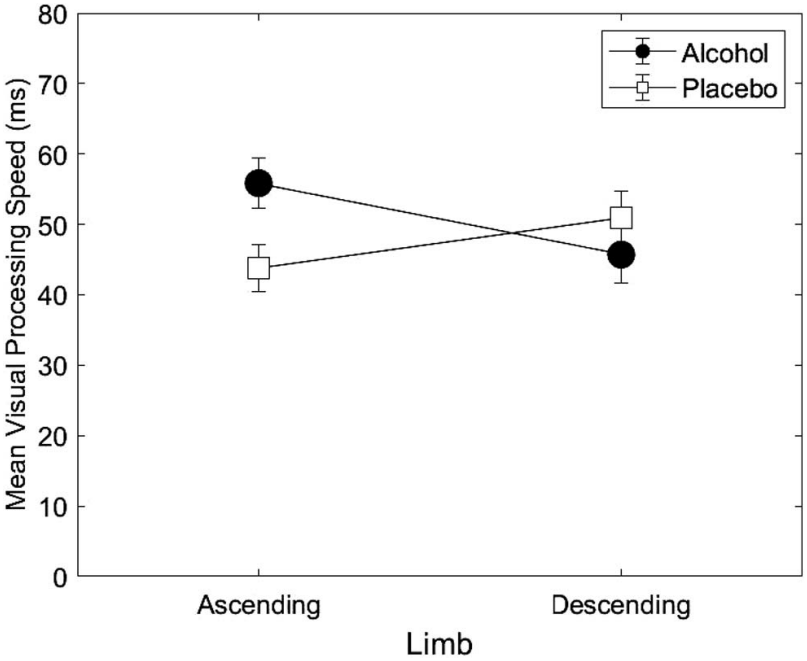


Figure 9. Adjusted mean and standard errors of visual information processing speed in dose and placebo groups on each limb.

SART.

To test for an effect of alcohol on response accuracy (errors of commission), RT and post-error-slowing, we compared scores between groups on each limb using one-way ANCOVAs, treating baseline scores as a covariate. An effect of alcohol was not found in any performance measure from the SART because the differences between groups on either limb were not statistically significant ($p > .05$; see Figure 10).

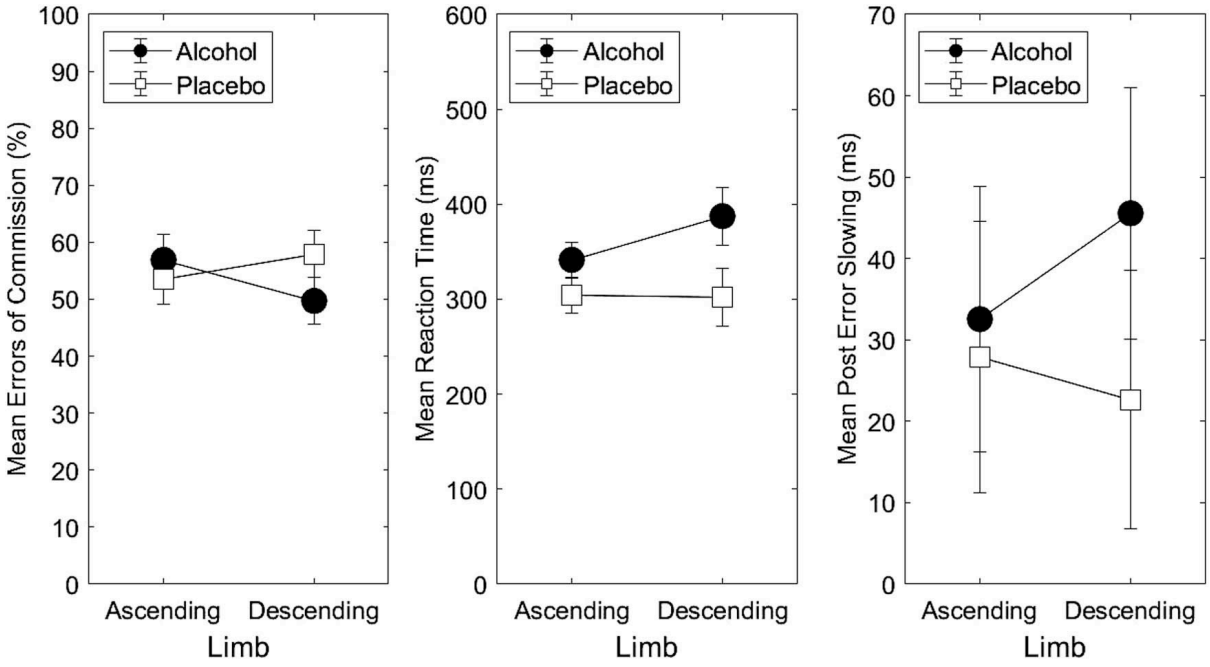


Figure 10. Adjusted scores and standard errors for all three Sustained Attention to Response Task performance measures in dose and placebo groups on each limb.

Discussion

This study examined changes in the dose effect of alcohol on subjective intoxication and performance in the ITT and SART between the ascending and descending limbs of the BAC curve when BAC was equivalent. Alcohol increased ratings of subjective intoxication and impaired performance on the ITT when BAC was ascending. However, performance on the SART was not found to be affected by alcohol. Consistent with an acute tolerance effect, the ratings of subjective intoxication and impairment on the ITT in the alcohol group decreased during the dose. Because BAC was equivalent at the times the measures were taken, it can be concluded that the dose effect decreased between the ascending and descending limb. Although ITT performance in the placebo

group also varied between limbs, likely due to fatigue or a similar extraneous effect, this can be assumed to have also affected the alcohol group because conditions were equivalent.

The finding of acute tolerance on ratings of intoxication adds to the already sizable body of literature that has reported acute tolerance to the subjective effects of alcohol. At a BAC of 0.05%, the degree of felt intoxication, relative to the maximum effect produced by the dose, diminished substantially between limbs within a period of 80 min. Testing with doses of alcohol is known to produce expectation effects, which were seen in this study in the ratings of subjective intoxication given by the placebo group. However, the substantial decrease in subjective intoxication ratings seen in the alcohol group was not seen in the placebo group, which suggests a decrease in the felt effects of alcohol independent of expectation effects.

The subjective effects of alcohol are important to consider because they are the most readily available cues for individuals to use to gauge their intoxication when deciding on their present drinking behavior. When individuals make the decision to continue drinking when intoxicated, or consider whether it is safe for them to drive while under the influence of alcohol, it is largely based on the degree of intoxication they are feeling at the time, and a decrease in subjective effects could cause underestimation of their current BAC or any functional impairment that does not also recover at a comparable rate. Acute tolerance to the subjective effects can then be seen as a likely contributor to excess consumption (Aston & Liguori, 2013; Earleywine & Erblich, 1996) and drink driving (Courtney & Polich, 2009). A BAC of 0.05% is used as the legal driving limit in many countries around the world. Because the feelings of intoxication produced at 0.05% have been shown to decrease, subjective feelings should be considered an unreliable gauge of intoxication. Public safety campaigns have not explicitly targeted awareness of acute tolerance as a factor to consider in responsible drinking. Given the reliable finding of acute tolerance to subjective effects, raising awareness of the effect is potentially of benefit.

To our knowledge, the present study is the first to examine the dose effect in the ITT when measures on both limbs were taken post-dose. The finding of acute tolerance in ITT performance is in contrast to that of Cash et al. (2015) and Peacock et al. (2015). As previously mentioned, the cumulative-dose protocol used in these past studies contrasts with the single-dose protocol used in the current study. The conflicting findings could suggest that acute tolerance develops only under fast, bolus doses, but the effect has been seen when cumulative dosing is used (Söderlund et al., 2005; Streufert et al., 1992) and has been seen to carry over into subsequent doses (Benton, Banks, & Vogler,

1982). The absence of acute tolerance that is often observed when using cumulative dosing protocols with the Mellanby paradigm can potentially be attributed to the comparison of effect between measures taken when participants are under the effect of different-sized doses. Despite BACs being equivalent when measures are taken on each limb, a portion of the entire dose is often given after the ascending limb measures when cumulative dosing protocols are used. As such, it is recommended that cumulative protocols be avoided when attempting to create conditions suitable for testing acute tolerance with the Mellanby paradigm. The differing findings of acute tolerance in ITT performance between these dose protocols does lend some support to the hypothesis that the development of acute tolerance is influenced by the rate the dose is consumed. (Comley & Dry, 2019). If the rate of consumption influences acute tolerance development, it would be worthy of further examination.

The finding of acute tolerance in a measure of information processing is consistent with previous studies, but the finding of an acute tolerance effect on the ITT is unique because it is the first measure of information processing to show the effect in performance other than the speed of response. Previous studies examining acute tolerance in information processing have used tasks that included motor speed as an aspect of performance. Alcohol was found to impair both speed and accuracy of performance, but acute tolerance was seen only in measures of speed (Schweizer et al., 2004, 2006). Although ITT performance does not directly measure accuracy, scoring lower minimum display times requires making accurate responses. Because the ITT is free from motor speed, the acute tolerance effect observed in this study can be attributed to the dose effect of alcohol on information processing speed decreasing. This finding suggests that information processing is a domain of behavior that shows acute tolerance to alcohol when it is measured free from the influence of motor speed performance and highlights the influence of the task used to measure the effect of alcohol on findings of acute tolerance in particular behavioral domains.

Evidence of acute tolerance to impairment in response inhibition was not found in this study, because performance in both the alcohol and placebo group was similar at all time points for all SART measures. Although the observed variance in post-error slowing in the SART appeared high, it was not dissimilar to that found in previous studies (Beu, Burns, & Baetu, 2019). Because the SART did not show any effect of alcohol, there was not sufficient impairment to show recovery as evidence of acute tolerance. The differential effect of alcohol between the two cognitive tasks used in this study highlights the variable nature of alcohol impairment. The finding is to some degree explained by information processing and response inhibition being associated with different areas of cortical

activation (Deary et al., 2004; O'Connor, Manly, Robertson, Hevenor, & Levine, 2004), because the acute effects of alcohol on cognition have been shown to be dependent on the brain region associated with specific functions (Van Skike, Goodlett, & Matthews, 2019). The lack of impairment may have been due to an insufficiently sized dose. However, Dry et al. (2012) previously demonstrated that performance accuracy in the SART was impaired at a BAC of 0.048%. A noticeable difference in methodology from the present study was that participants received additional alcohol immediately before completing the task at a BAC of 0.048%.

The magnitude of the acute tolerance observed in ITT performance and ratings of subjective intoxication cannot be equated between measures with such obvious conceptual differences. The observed change (mean difference) in subjective intoxication ratings of 8 mm cannot be equated with the 7-ms change in stimulus duration. However, it can be concluded that the effect of a BAC of 0.05% on both these measures was less later in the dose. It has previously been suggested that the impairment to driving caused by alcohol may recover due to acute tolerance (Laverty, 1989). ITT performance could be considered as a measure of a cognitive component of driving, because decisions while driving need to be made in response to information that must be processed, for example, responding to a car's turn signal (Gregory, Callaghan, Nettelbeck, & Wilson, 2009). Although it could be inferred from these findings that impairment to cognitive functions associated with driving recover while BAC remains elevated, the larger body of literature suggests otherwise. This is likely because driving is a multifaceted task of which information processing speed is only one component. Studies testing acute tolerance in driving simulator performance have not found that impairment at a given BAC diminished during the dose (Gengo et al., 1990; Marczinski & Fillmore, 2009; Starkey & Charlton, 2014; Weafer & Fillmore, 2012). Also, autopsy data show that road accidents are more prevalent when victims are on the descending limb of the BAC curve (Lahti et al., 2014). This suggests that although cognitive performance in domains such as information processing speed may show statistically significant recovery from alcohol, it is unlikely to be clinically or ecologically significant to the degree that driving with an elevated BAC becomes safe.

An inherent limitation in comparing the dose effect between limbs of the BAC curve is the lack of control over the direction of BAC change. Although this study appropriately matched the time of measures on each limb to control for changes in BAC, the direction of the BAC change differed at the time of each measure. Other methods of modelling the dose effect, such as those used by Hendershot et al. (2015), Radlow and Hurst (1985), and Vogel- Sprott and Fillmore (1993), do not have this

limitation. Observing the development of acute tolerance in information processing using such methods could confirm that the effect occurs independently of BAC change direction. Another limitation of this study is the restricted generalizability of the sample. As is common in this area of research, the entire sample was drawn from a population of undergraduate psychology students. There is limited research on acute tolerance using a more generalizable sample. Given the widespread use of alcohol in the general population as well as its importance in specific populations such as those with alcohol use disorder, investigation of the effect outside of university populations is warranted. A potential limitation in this study was the inclusion of smokers. Nicotine has been shown to have cognitive enhancing effects (Valentine & Sofuoglu, 2018), which could have been present in this study but were not controlled for, because data on nicotine use were not collected. Because it is a common practice to both drink alcohol and smoke in the same sitting, research specifically on the effect of nicotine on acute alcohol tolerance should be conducted. Finally, this study tested participants under a bolus single dose, which is somewhat removed from real-world drinking patterns. Although such a dose is appropriate for testing for acute tolerance with the Mellanby paradigm, further examination of the effect under cumulative, more naturalistic doses should be conducted but with paradigms more appropriate than Mellanby's.

In summary, this study found that alcohol-impaired performance in speed of information processing as measured by the ITT. In addition, consistent with an acute tolerance effect, the degree, of impairment at a BAC of approximately 0.05% decreased during the dose. As far as the authors are aware, this was the first study to find acute tolerance in a measure of information processing that is free from motor speed performance. Also consistent with acute tolerance, ratings of felt intoxication differed greatly between limbs at a BAC of 0.05%. The subjective effects of alcohol are strong determinants of drinking behavior, and their variability should be considered in public safety.

References

Aston, E. R., & Liguori, A. (2013). Self-estimation of blood alcohol concentration: A review. *Addictive Behaviors, 38,* 1944–1951. http://dx.doi.org/10.1016/j.addbeh.2012.12.017

Beu, N. D., Burns, N. R., & Baetu, I. (2019). Polymorphisms in dopaminergic genes predict proactive processes of response inhibition. *European Journal of Neuroscience, 49,* 1127–1148. http://dx.doi.org/10.1111/ejn.14323

Benton, R. P., Banks, W. P., & Vogler, R. E. (1982). Carryover of tolerance to alcohol in moderate drinkers. *Journal of Studies on Alcohol, 43,* 1137–1148.

Calhoun, V. D., Pekar, J. J., & Pearlson, G. D. (2004). Alcohol intoxication effects on simulated driving: Exploring alcohol-dose effects on brain activation using functional MRI. *Neuropsychopharmacology, 29,* 2097–2107. http://dx.doi.org/10.1038/sj.npp.1300543

Cash, C., Peacock, A., Barrington, H., Sinnett, N., & Bruno, R. (2015). Detecting impairment: Sensitive cognitive measures of dose-related acute alcohol intoxication. *Journal of Psychopharmacology, 29,* 436– 446. http://dx.doi.org/10.1177/0269881115570080

Comley, R. E., & Dry, M. J. (2019). Acute behavioral tolerance to alcohol. *Experimental and Clinical Psychopharmacology*. Advance online publication. http://dx.doi.org/10.1037/pha0000296

Conigrave, K. M., Hall, W. D., & Saunders, J. B. (1995). The AUDIT questionnaire: Choosing a cut-off score: Alcohol Use Disorder Identification Test. *Addiction, 90,* 1349–1356.

Courtney, K. E., & Polich, J. (2009). Binge drinking in young adults: Data, definitions, and determinants. *Psychological Bulletin, 135,* 142–156. http://dx.doi.org/10.1037/a0014414

Crow, K. E., & Batt, R. D. (1989). *Human metabolism of alcohol.* Boca Raton, FL: CRC Press.

Deary, I. J., Simonotto, E., Meyer, M., Marshall, A., Marshall, I., Goddard, N., & Wardlaw, J. M. (2004). The functional anatomy of inspection time: An event-related fMRI study. *NeuroImage, 22,* 1466–1479. http://dx.doi.org/10.1016/j.neuroimage.2004.03.047

Dry, M. J., Burns, N. R., Nettelbeck, T., Farquharson, A. L., & White, J. M. (2012). Dose-related effects of alcohol on cognitive functioning. *PLoS ONE, 7*(11), e50977. http://dx.doi.org/10.1371/journal.pone.0050977

Earleywine, M., & Erblich, J. (1996). A confirmed factor structure for the Biphasic Alcohol Effects Scale. *Experimental and Clinical Psychopharmacology, 4,* 107–113. http://dx.doi.org/10.1037/1064-1297.4.1.107

Fillmore, M. T., Marczinski, C. A., & Bowman, A. M. (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *Journal of Studies on Alcohol, 66,* 663–672. http://dx.doi.org/10.15288/jsa.2005.66.663

Fillmore, M. T., & Vogel-Sprott, M. (1998). Behavioral impairment under alcohol: Cognitive and pharmacokinetic factors. *Alcoholism: Clinical and Experimental Research, 22,* 1476–1482.

Fillmore, M. T., & Weafer, J. (2012). Acute tolerance to alcohol in at-risk binge drinkers. *Psychology of Addictive Behaviors, 26,* 693–702. http://dx.doi.org/10.1037/a0026110

Gengo, F. M., Gabos, C., Straley, C., & Manning, C. (1990). The pharmacodynamics of ethanol: Effects on performance and judgment. *Journal of Clinical Pharmacology, 30,* 748–754. http://dx.doi.org/10.1002/j.1552-4604.1990.tb03638.x

Ginsburg, B. C., Martinez, G., Friesenhahn, G., Javors, M., & Lamb, R. J. (2008). Acute tolerance to rate-decreasing effects of single doses of ethanol. *Physiology & Behavior, 94,* 374–383. http://dx.doi.org/10.1016/j.physbeh.2008.01.026

Gregory, T., Callaghan, A., Nettelbeck, T., & Wilson, C. (2009). Inspection time predicts individual differences in everyday functioning among elderly adults: Testing discriminant validity. *Australasian Journal on Ageing, 28,* 87–92. http://dx.doi.org/10.1111/j.1741-6612.2009.00366.x

Hart, C. L., Ksir, C., & Ray, O. S. (2013). *Drugs, society & human behavior*. New York, NY: McGraw-Hill.

Hendershot, C. S., Wardell, J. D., Strang, N. M., Markovich, M. S., Claus, E. D., & Ramchandani, V. A. (2015). Application of an alcohol clamp paradigm to examine inhibitory control, subjective responses, and acute tolerance in late adolescence. *Experimental and Clinical Psychopharmacology, 23,* 147–158. http://dx.doi.org/10.1037/pha0000017

Holland, M. G., & Ferner, R. E. (2017). A systematic review of the evidence for acute tolerance to alcohol—The "Mellanby effect." *Clinical*

Toxicology, 55, 545–556. http://dx.doi.org/10.1080/15563650.2017.1296576

Jensen, A. R. (2006). *Clocking the mind mental chronometry and individual differences* (1st ed.). Amsterdam, the Netherlands: Elsevier.

Lahti, R. A., Pitkäniemi, J., Jones, A. W., Sajantila, A., Poikolainen, K., & Vuori, E. (2014). Cause and manner of death and phase of the blood alcohol curve. *Forensic Science International, 244,* 306–312. http://dx.doi.org/10.1016/j.forsciint.2014.09.015

Laverty, R. (1989). Tolerance to alcohol and its relationship to dependence. In K. E. Crow & R. D. Batt (Eds.), *Human metabolism of alcohol* (Vol. 3, pp. 175–188). Boca Raton, FL: CRC Press.

Manly, T., Robertson, I. H., Galloway, M., & Hawkins, K. (1999). The absent mind: Further investigations of sustained attention to response. *Neuropsychologia, 37,* 661– 670. http://dx.doi.org/10.1016/S0028-3932 (98)00127-4

Marczinski, C. A., & Fillmore, M. T. (2009). Acute alcohol tolerance on subjective intoxication and simulated driving performance in binge drinkers. *Psychology of Addictive Behaviors, 23,* 238–247. http://dx.doi.org/10.1037/a0014633

Mellanby, E. (1919). *Alcohol: Its absorption into and disappearance from the blood under different conditions* (Special Report Series No. 31). London, United Kingdom: Medical Research Committee.

Miller, M. A., & Fillmore, M. T. (2014). Protracted impairment of impulse control under an acute dose of alcohol: A time-course analysis. *Addictive Behaviors, 39,* 1589–1596. http://dx.doi.org/10.1016/j.addbeh.2013.10.035

Müller, C. P., & Schumann, G. (2011). Drugs as instruments: A new framework for non-addictive psychoactive drug use. *Behavioral and*

Brain Sciences, 34, 293–310. http://dx.doi.org/10.1017/S0140525 X11000057

O'Connor, C., Manly, T., Robertson, I. H., Hevenor, S. J., & Levine, B. (2004). An fMRI of sustained attention with endogenous and exogenous engagement. *Brain and Cognition, 54,* 133–135.

Ostling, E. W., & Fillmore, M. T. (2010). Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior. *Psychopharmacology, 212,* 465–473. http://dx.doi.org/10.1007/s00213-010-1972-y

Peacock, A., Cash, C., & Bruno, R. (2015). Cognitive impairment following consumption of alcohol with and without energy drinks. *Alcoholism: Clinical and Experimental Research, 39,* 733–742. http://dx.doi.org/10.1111/acer.12680

Pohorecky, L. A., & Brick, J. (1988). Pharmacology of ethanol. *Pharmacology & Therapeutics, 36,* 335–427. http://dx.doi.org/10.1016/0163-7258 (88)90109-X

Preiss, A., & Burns, N. (2012). Accurately measuring inspection time with computers. *International Journal of Intelligence Science, 2,* 96–102. http://dx.doi.org/10.4236/ijis.2012.24013

Radlow, R., & Hurst, P. M. (1985). Temporal relations between blood alcohol concentration and alcohol effect: An experiment with human subjects. *Psychopharmacology, 85,* 260–266. http://dx.doi.org/10.1007BF00428184

Rigter, H., & Crabbe, J. C. (1980). *Alcohol tolerance and dependence*. New York, NY: Elsevier/North-Holland Biomedical Press.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). "Oops!": Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35,* 747–758. http://dx.doi.org/10.1016/S0028-3932 (97)00015-8

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction, 88,* 791–804. http://dx.doi.org/10.1111/j.1360-0443.1993.tb02093.x

Schweizer, T. A., Jolicoeur, P., Vogel-Sprott, M., & Dixon, M. J. (2004). Fast, but error-prone, responses during acute alcohol intoxication: Effects of stimulus-response mapping complexity. *Alcoholism: Clinical and Experimental Research, 28,* 643–649. http://dx.doi.org/10.1097/01 .ALC.0000121652.84754.30

Schweizer, T. A., & Vogel-Sprott, M. (2008). Alcohol-impaired speed and accuracy of cognitive functions: A review of acute tolerance and recovery of cognitive performance. *Experimental and Clinical Psychopharmacology, 16,* 240–250. http://dx.doi.org/10.1037/1064 1297.16.3.240

Schweizer, T. A., Vogel-Sprott, M., Danckert, J., Roy, E. A., Skakum, A., & Broderick, C. E. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacology, 31,* 1301–1309. http://dx.doi.org/10 .1038/sj.npp.1300941

Söderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology, 182,* 305–317. http://dx.doi.org/10.1007/s00213-005-0096-2

Starkey, N. J., & Charlton, S. G. (2014). The effects of moderate alcohol concentrations on driving and cognitive performance during ascending and descending blood alcohol concentrations. *Human Psychopharmacology: Clinical and Experimental, 29,* 370–383. http://dx.doi.org/10.1002/hup.2415

Streufert, S., Pogash, R. M., Roache, J., Gingrich, D., Landis, R., Severs, W., . . . Kantner, A. (1992). Effects of alcohol intoxication on risk taking, strategy, and error rate in visuomotor performance. *Journal of Applied Psychology, 77,* 515–524. http://dx.doi.org/10.1037/00219010 .77.4.515

Sullivan, E. V., & Pfefferbaum, A. (2014). *Alcohol and the central nervous system: Handbook of clinical neurology*. Oxford, United Kingdom: Elsevier.

Valentine, G., & Sofuoglu, M. (2018). Cognitive effects of nicotine: Recent progress. *Current Neuropharmacology, 16,* 403–414. http://dx.doi.org/10.2174/1570159X15666171103152136

Van Skike, C. E., Goodlett, C., & Matthews, D. B. (2019). Acute alcohol and cognition: Remembering what it causes us to forget. *Alcohol, 79,* 105–125. http://dx.doi.org/10.1016/j.alcohol.2019.03.006

Vengeliene, V., Bilbao, A., Molander, A., & Spanagel, R. (2008). Neuropharmacology of alcohol addiction. *British Journal of Pharmacology, 154,* 299–315. http://dx.doi.org/10.1038/bjp.2008.30

Vickers, D., Nettelbeck, T., & Willson, R. J. (1972). Perceptual indices of performance: The measurement of "inspection time" and "noise" in the visual system. *Perception, 1,* 263–295. http://dx.doi.org/10.1068/p010263

Vogel-Sprott, M., & Fillmore, M. T. (1993). Impairment and recovery under repeated doses of alcohol: Effects of response-outcomes. *Pharmacology, Biochemistry, and Behavior, 45,* 59–63. http://dx.doi.org/10.1016/0091-3057 (93)90086-9

Vogel-Sprott, M., & Sdao-Jarvie, K. (1989). Learning alcohol tolerance: The contribution of response expectancies. *Psychopharmacology, 98,* 289–296. http://dx.doi.org/10.1007/BF00451677

Weafer, J., & Fillmore, M. T. (2012). Acute tolerance to alcohol impairment of behavioral and cognitive mechanisms related to driving: Drinking and driving on the descending limb. *Psychopharmacology, 220,* 697–706. http://dx.doi.org/10.1007/s00213-011-2519-6

Weissenborn, R., & Duka, T. (2003). Acute alcohol effects on cognitive function in social drinkers: Their relationship to drinking habits. *Psychopharmacology, 165,* 306 –312. http://dx.doi.org/10.1007/s00213-002-1281-1

Statement of Authorship

Title of Paper	Acute tolerance to alcohol in objective and subjective measures
Publication Status ☑	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Submitted to 'Psychopharmacology'

Principal Author

Name of Principal Author (Candidate)	Ross Edward Comley		
Contribution to the Paper	Experimental design, data collection, analysis, and interpretation, drafting of manuscript		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19/10/2020

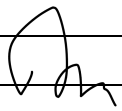
Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Matthew Dry		
Contribution to the Paper	General guidence as supervisor		
Signature		Date	20-10-20

3.3 Manuscript: Acute Tolerance to Alcohol in Objective and Subjective Measures

Acute Tolerance to Alcohol in Objective and Subjective Measures

R. Edward Comley

and Matthew J. Dry

Abstract

Acute tolerance to alcohol is a decrease in the dose-effect occurring within the duration of a single dose. Although measures of the subjective effects of alcohol reliably show acute tolerance, objective behavioural measures like cognitive tasks show the effect less often and it remains uncertain which cognitive domains are susceptible to it. It is also unclear what influence the size of the alcohol dose has on the development of acute tolerance. This study examined acute tolerance under two different dose sizes, in subjective intoxication and in two cognitive domains: response inhibition measured using the Stop-Signal Task paradigm (SST), and psychomotor and executive decision making speed measured using the Multiple Choice Reaction Time task (MCRT). One hundred and eight participants were allocated to one of four dose conditions. Either a high or low active dose, or a matched placebo dose. After baseline measures, the high active dose group was given alcohol to produce a peak BAC of 0.08%, the low active dose group was given alcohol to produce a peak BAC of 0.06%, and placebo group received a placebo beverage. Performance on the SST and MCRT was measured twice during the course of the dose at a BAC of .05%, once when BAC was ascending and again when descending. The placebo group was tested at equivalent times. In the low-dose condition, alcohol impaired reactive-inhibition in the SST and response speed in the MCRT on the ascending limb of the BAC curve. In the high-dose condition, alcohol impaired accuracy in the MCRT on the ascending limb. However, acute tolerance was unable to be confirmed for these measures. Acute tolerance to subjective intoxication was only found in the high dose condition.

Introduction

The unique place that alcohol occupies in society necessitates understanding its effect on behaviour. Alcohol consumption is not unique to humans (Dominy, 2004; Myers & Veale, 1972), but its deliberate production from harvested produce is (McGovern, 2009). Despite alcohol having had a central place in human civilization for at least as long as agriculture, its consumption has often been associated with negative outcomes and alcohol consumption remains the cause of many social, health and behavioural problems (Hames, 2014). One in every 20 deaths can be attributed to alcohol (WHO, 2014) and it is a prevalent feature in violent crimes and road traffic accidents (Gopalakrishnan, 2012; McClelland & Teplin, 2001). The negative effects of alcohol consumption could potentially be mitigated by improving our understanding of how the drug affects behaviour.

Because the dose-response of alcohol is generally linear, the strength of the effect that alcohol has on behaviour is largely determined by the size of the dose (Hart, Ksir, & Ray, 2013). As the size of the dose increases the magnitude of the effects also increases. This characteristic of alcohol (among other drugs) allows for the prescription of patterns of consumption in terms of dose sizes (i.e. no more than four standard drinks on any one occasion; NHMRC, 2009), as well as justification for legal blood alcohol limits while driving (Meyer & Quenzer, 2005). However, variations in the dose-effect (the strength of the effect relative to the size of the dose) of alcohol are commonly found. Doses of equal size are often seen to produce different strengths of effect within individuals across different situations (Fillmore & Vogel-Sprott, 1998; Kalant, 1996).

A decrease in the dose-effect is called *tolerance*, which is characterised by doses producing weaker effects relative to previous doses of equal size, and effects of a given magnitude requiring larger doses to be produced (Vogel-Sprott & Sdao-Jarvie, 1989). The time frame in which the decrease in dose-effect is observed is used to classify the type of tolerance (Kalant, 1996). *Acute tolerance* is a decrease in the dose-effect observed on a short time scale; specifically, within the duration of a single dose. Changes in the dose-effect occurring during a dose can be observed using the blood-alcohol concentration (BAC) as a contemporaneous measure of dose size, and examining the change in the strength of the drug-effect relative to the BAC (Rigter & Crabbe, 1980). Because changes in the BAC can cause changes in the strength of the drug-effect, changes in BAC that occur during the course of the dose need to be controlled for in order to accurately assess other changes in the drug-effect (Martin & Moss, 1993).

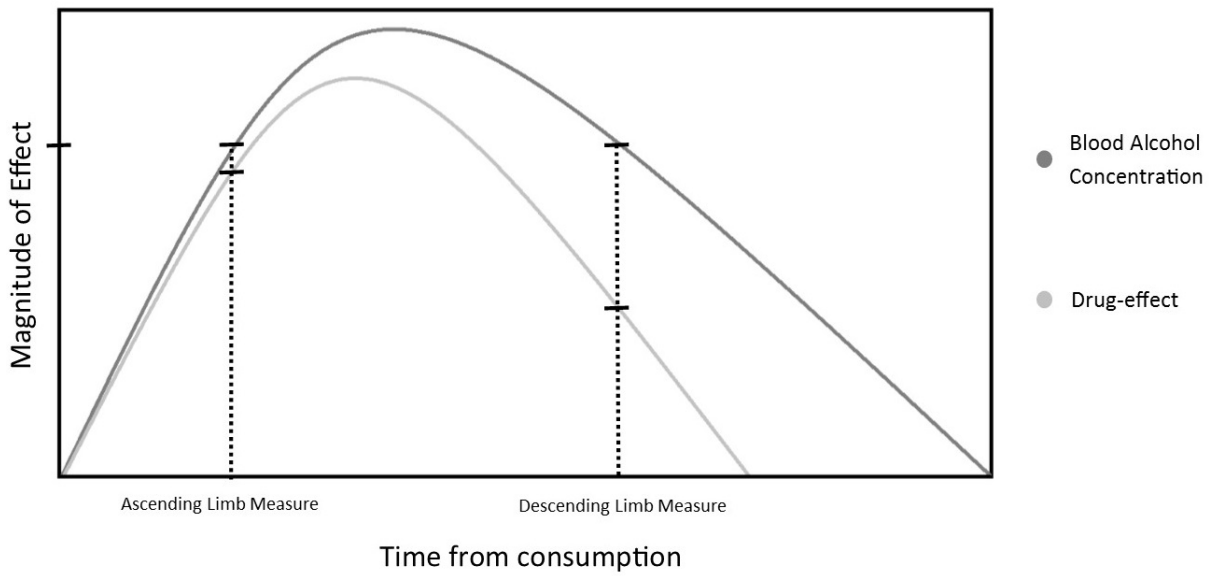


Figure 11. Limb comparison for BAC and Drug-effect showing a decrease in drug-effect between limbs at equivalent BAC's

The most common way of controlling for changes in BAC when examining changes in dose-effect has been the limb comparison paradigm utilised by Mellanby, who first reported an acute tolerance effect in 1919[16] As Figure 11 illustrates, the course of BAC from a single dose of alcohol follows a reliable two-limbed (ascending & descending) curve increasing from zero to peak, and then decreasing from peak back to zero. Consequently, BACs lower than the peak concentration occur twice during a single dose, once on the ascending limb and again on the descending limb (Crow & Batt, 1989). By comparing the drug-effect between the two limbs of the dose curve at times when BAC is equivalent the need to account for changes in BAC is removed.

Acute tolerance is an important factor to consider in the management of alcohol-related harms because the rapid nature of the decrease in effect means the dose-effect of alcohol varies *during* the time course of a dose, therefore the strength of the effects produced by a dose of alcohol at a given time cannot be predicted solely by the BAC (Fillmore & Vogel-Sprott, 1998). Estimates of the acute effects of alcohol would be more accurate if changes in the dose-effect such as acute tolerance were accounted for. Although findings of acute tolerance are prevalent in studies that use an experimental paradigm in which it can be observed, the cognitive processes it affects remain unclear as the effect does not seem to develop uniformly across different behavioural domains. While acute tolerance is

[16] Note: Mellanby never used the term "acute tolerance".

reliably found in subjective measures of the effect of alcohol, in which participants report the felt or perceived effects of alcohol, data from objective behavioural measures have only sometimes demonstrated the effect (for a review, see Comley & Dry, 2020-a).

In a real-world scenario, a difference in acute tolerance between subjective and objective effects could result in a consumer feeling that they had recovered from the deleterious effects of alcohol while they actually still remained impaired. Because of the inconsistency in acute tolerance observed between different behavioural measures, the primary aim of the current study is to use Mellanby's limb-comparison paradigm to test for acute tolerance in subjective intoxication and in objective measures of behavioural performance known to be affected by alcohol intoxication. Since cognitive domains that require rapid, higher-order processing, psychomotor coordination and inhibition are likely to map onto real-world experiences of alcohol-induced performance impairment (i.e. driving), they provide an ecologically valid context in which to potentially reconcile the subjective/objective incongruence described above.

Response inhibition is a cognitive domain reliably shown to be impaired by alcohol (Abroms, Fillmore, & Marczinski, 2003; Dry, Burns, Nettelbeck, Farquharson, & White, 2012; Fillmore, Marczinski, & Bowman, 2005; Weafer & Fillmore, 2012), yet previous investigations of acute tolerance in response inhibition tasks have shown that the domain is somewhat resistant to the effect. The response inhibition tasks previously used to examine acute tolerance have used both speed and accuracy as performance measures. Acute tolerance has been found in measures of speed (reaction time), while measures of accuracy are yet to show the effect (Schweizer, Jolicœur, Vogel-Sprott, & Dixon, 2004). Response inhibition is driven by two processes: reactive inhibition and proactive inhibition (Zhang & Iwaki, 2019). Because the response inhibition tasks previously used to examine acute tolerance have not delineated these two processes, the absence of the effect in measures of accuracy could be explained by differential recruitment of these two processes that have been shown to vary as a function of task demands (Beu, Burns. & Baetu, in prep.). If acute tolerance is unique to one component of response inhibition, tasks combining both components in performance measures may be unable to detect the effect. The current study examines acute tolerance in response inhibition using the Stop-Signal Task paradigm (Logan, 1994), which is a unique measure of response inhibition in that it can specifically measure both proactive and reactive response inhibition.

Unlike tasks previously used to examine acute tolerance in response inhibition, the Stop-Signal Task does not provide a valid measure of performance speed. As acute tolerance is often seen to develop in measures of speed but not in measures of accuracy, a measure of reaction time was also included in this study. Furthermore, the ecological validity of including a task that requires rapid action selection and generation with an implicit speed-accuracy trade-off has clear relevance to understanding intoxicated behaviour. The Choice Reaction Time task (MCRT) has previously shown acute tolerance to alcohol (Miller & Fillmore, 2014) and was included in the current study to provide a measure of psychomotor and executive decision making speed.

Aside from the type of measure used to test for the effect, another potential factor of influence in findings of acute tolerance is the size of the dose under which the effect is tested (Comley & Dry, 2020-a). Previous studies into the effect of dose size on acute tolerance have been few, and have been inconsistent in both their methods and findings (Earleywine & Erblich, 1996; Gengo, Gabos, Straley, & Manning, 1990; Nicholson et al., 1992; Starkey & Charlton, 2014; Streufert et al., 1992; Tupler, Hege, & Ellinwood, 1995). Because of the potential influence of the size of the dose on acute tolerance, this study tests for and compares the effect between two different dose sizes.

Previous studies that have tested for acute tolerance using the Mellanby paradigm have not used uniform methods to show an effect of alcohol or recovery from it. An effect of alcohol has been demonstrated with comparisons both between (alcohol vs placebo) and within (pre- vs post-dose) groups (Cash, Peacock, Barrington, Sinnett, & Bruno, 2015; Dougherty, Bjork, & Bennett, 1998; Hiltunen, 1997). A decrease in the effect of alcohol is commonly tested for by examining changes in the size of the drug-effect between limbs; but some studies have used the absence of an impairment on the descending limb after the presence of impairment on the ascending limb as evidence of acute tolerance, without considering the variance of the change in impairment. The inconsistency in the methods for testing data from the Mellanby paradigm has limited the comparisons that can be made between studies and raises concerns about the reliability of the effect.

The present study used three criteria to test for the presence of acute tolerance in the Mellanby paradigm. First, an effect of alcohol must be observed on a behavioural measure on the ascending limb of the BAC curve, evidenced by a difference between a dosed alcohol group and a placebo control group on a given measure. Second, the size of the effect on the descending limb must be smaller than on the ascending limb (at an equivalent BAC); and, third, a statistically significant

interaction between the limb and the group must be observed in order to confirm the change in dose-effect between limbs. If these three criteria are satisfied and acute tolerance is established, the strength of the effect will be compared between dose sizes.

Method

Participants

This study was approved by the University of Adelaide's Human Research Ethics Committee. To find an effect size similar to the acute tolerance previously found in objective measures (F = 0.25; Comley & Dry, 2020-b) with power at 0.95 and alpha 0.05, our sample size needed to be N = 54 in each dose condition. One hundred and eight first-year university students (59 women), aged 18-33 years (M = 19.7, SD = 2.78) were recruited to take part in the study via an online scheduling system which grants course credit in return for participation. Eligibility to participate was subject to the following criteria:

(i) aged 18–45 years

(ii) not currently pregnant or lactating

(iii) no major medical or psychiatric conditions

(iv) no uncorrected visual disorders

(v) no dependence on any substance (excluding nicotine)

(vi) fluent in English

(vii) no history of alcohol-related problems

(viii) not taking medication having a stimulative or sedative action

(ix) had consumed at least three alcoholic beverages on at least one occasion in the past month

(x) had not consumed alcohol or other drugs (except nicotine) in the previous 24 hours

The age range was limited to ensure that participants were of legal drinking age, but unlikely to be affected in their task performance by well-established age-related cognitive decline. Criterion ix was included to ensure that participants were familiar with the doses of alcohol being given. Participants' level of risky drinking behaviour was assessed using the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT is a 10-item questionnaire reporting the occurrence and severity of alcohol-related problems during the twelve months prior to evaluation (Saunders, Aasland,

Babor, De la Fuente, & Grant, 1993). Participants who scored 15 or higher were to be excluded, but no participant reached this criterion level.

Measures

All cognitive tasks were programmed at the University of Adelaide and installed on Windows 10 (Microsoft Corporation, Redmond, USA) machines. Tasks included onscreen instructions. Peripheral computer hardware was standardised across machines; an HP corded mouse (1000 dpi) and keyboard were used (Hewlett-Packard Co., Palo Alto, USA). General demographic information for each participant was collected via a self-report questionnaire. Responses regarding gender and body weight were used to calculate alcohol doses. A digital scale was used to measure participants' body weight.

Stop Signal Task.

The Stop Signal Task is a computerised cognitive performance task that measures both proactive and reactive inhibition by adjusting the time a stop signal is delayed using participant's response times (RT), to produce a trial-by-trial error probability of 50% (i.e., P (Error) = 0.5) using a Bayesian adaptive staircase function (see Livesey and Livesey, 2016). We use a novel adaptation of this task that is fully described and validated elsewhere (Beu, Burns, & Baetu, in prep.), and which captures not only the distinction between reactive and proactive inhibition but two conceptually distinct types of proactive inhibition. In this version of the task (see Figure 12), participants are presented with a target symbol (a white arrow) facing either Left or Right, embedded in either an Orange or Purple circle in the centre of the screen. Participants are instructed to respond to the target symbol by pressing one of the corresponding keys which roughly correspond to the Left and Right side of the keyboard as quickly as they can without sacrificing accuracy. In some trials, the target symbol is changed to a stop-signal (an arrow facing the opposite direction appears on the target symbol arrow) after a delay (the Stop-Signal Delay; SSD), and in which case, participants are instructed to withhold their response. The colour of the circle containing the Left- or Right-facing arrow indicates the probability of a stop-signal appearing (Orange = 20%, Purple= 50%). This detail is given to participants in task instructions. The task consists of 320 randomly-ordered trials, equally distributed between colour condition and arrow direction (i.e., 80 trials for each Stop-Signal probability condition and arrow-direction combination), with a random inter-trial-interval between two and eight seconds. Each Stop trial's SSD is determined by a Bayesian adaptive staircase algorithm that adjusts the delay

by a stepwise duration, to minimise entropy for each subsequent trial as a function of Go RT and previous failed Stop attempt RT. For each participant, the first SSD is 300 msec and adjusts to their performance within an operationally minimal number of Stop trials (for full descriptions, see Livesey & Livesey, 2015; Beu, Burns, & Baetu, in prep.).

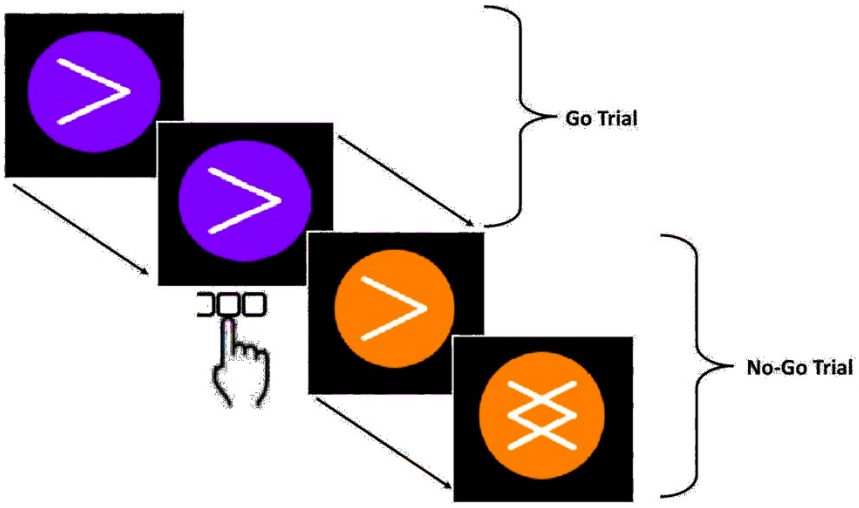


Figure 12. Two complete Stop Signal Task trials, one 50% condition, and one 20% condition. The first shows a Go trial in which participants respond to the stimulus. The second shows a No-Go trial where the target symbol changes in which participants should inhibit their response.

The measure of reactive inhibition is the Stop Signal Reaction Time (SSRT), which is derived by subtracting the critical SSD from the RT of incorrect Go trials for each probability condition. Proactive inhibition is measured in two ways. Probabilistic proactive inhibition is calculated from the difference in Go RT between 20% and 50% conditions (presumably reflecting additional caution in responding where a Stop-signal is more likely to occur). Remedial proactive inhibition is conceptualised here as post-error slowing (PES), which is generally measured by subtracting the average RT of four Go trials before an error from the average RT of four Go trials after an error.

Multiple choice reaction time.

The MCRT is a computerised task which measures psychomotor and executive decision making speed, specifically, the speed with which the test-taker is able to correctly select from an array of four possible responses and enact a simple motor response. Participants are presented with four white square frames displayed on a black screen. The target stimulus is pseudorandomly presented in one of those four squares as a solid white square filling the entirety of the frame. Inter-trial-intervals

vary with equiprobability between two and eight seconds. Participants are instructed to press one of four keys ([A], [S], [K], or [L]) corresponding to the box in which the stimulus appears (see Figure 13). The stimulus remains presented on the screen until a response is made. There are 40 trials. The task measures response accuracy from the number of correct responses, and reaction time using the median response time for correct responses excluding the first response.

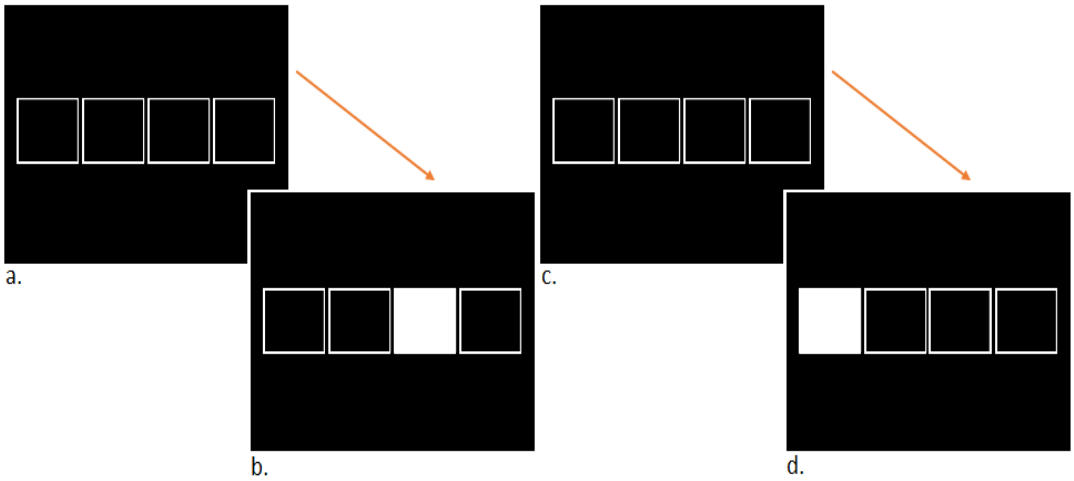


*Figure 13.*Two MCRT trials showing non-target ready state stimuli (a; c) and during target stimuli presentation (b; d) for which "k" and "a" keypresses would be the correct responses.

Subjective intoxication.

Subjective effects of alcohol were measured using a visual analogue scale (VAS) labelled "level of felt intoxication". A 100mm long black line was printed on a length of paper, with each end anchored left to right from "not at all" to "very much". Participants were instructed to mark a vertical line through the scale at the point which equated to their current feelings of intoxication. Ratings were recorded as mm from baseline.

Breathalyser.

BAC was measured from breath samples using a standardised Breathalyzer (Lion brand model 500P). Note that readings are reported as BAC and not Breath Alcohol Concentration (BrAC), as the Breathalyzer calculates BrAC to give readings as BAC.

Procedure

Participants were told at the time of their registration to fast for the four hours prior to their session after eating a normal breakfast, and to refrain from consuming alcohol or other drugs (except nicotine) for 24 hours prior to their participation. Participants were randomly pre-allocated to either a

high dose (n = 27), low dose (n = 27), or one of two placebo-control conditions (n = 54), each (n = 27) anchored to one of the active dose conditions. Participants arrived at the laboratory at approximately 12 pm and were briefed on the procedure, the nature of the measures and the effects of alcohol. Once briefed, participants voluntarily gave informed consent and completed the AUDIT and demographic questionnaire. To ensure that participants BAC was 0% when the procedure began a baseline breath alcohol measure was taken, and baseline ratings of subjective intoxication were taken with the VAS to familiarise participants with the measures. Baseline trials of the Stop Signal Task and the MCRT were then completed by the participants. The baseline scores were used to control for individual differences in performance. During this time, the experimenter calculated and prepared beverages with specific doses for each participant. Those in the alcohol group were given alcohol in the form of vodka (40% alcohol v/v) mixed with orange juice in a 2:9 mix. Doses in the alcohol group were calculated using the Widmark equation (Watson, Watson, & Batt, 1981), which calculates the volume of alcohol needed to raise an individual's BAC to a given level based on the participant's sex and body-weight. Doses in the low-dose condition were calculated to produce a peak BAC of 0.06%. In the high-dose condition, doses were calculated to produce a peak BAC of 0.08%.

Participants in the placebo-control groups received an equal volume of juice with a less than effective dose of alcohol. To give the impression that the placebo beverage contained a dose of alcohol 3 ml of vodka was coated on the rim of the cup and floated on the surface of the drink. Beverages in both conditions were equally divided into three cups, which were served at four-minute increments. Participants were instructed to drink each cup at a steady pace over four minutes, and that the beverage may or may not contain alcohol. After beverages had been drunk participants were given spring water to rinse their mouths and sip. BAC measures were taken repeatedly to follow the BAC. Subjective intoxication ratings were also taken with each BAC measure. Ten minutes after the beverages had been consumed, the Stop Signal Task and MCRT were administered for the second time. Once BAC had peaked and then declined back to approximately 0.05%, participants were again tested on the Stop Signal Task and MCRT. Each participant in the placebo-control group was anchored to a participant in the corresponding dose group and tested at equivalent times post-consumption. Light snacks were served to participants after the descending limb trials. Participants remained until BAC<0.01%, after which time they were debriefed and permitted to leave.

Data Analysis

Analyses were conducted using IBM SPSS Statistics 22 (IBM Inc., Armonk, NY, US). For Stop Signal Task and MCRT performance in each dose condition, the effect of alcohol on each limb was examined by comparing scores between matched dose and placebo conditions using one-way ANCOVAs, treating baseline scores as a covariate. If an effect of alcohol was found on the ascending limb and this effect was smaller on the descending limb then an interaction between dose-condition and limb was tested using a 2 (group) × 2 (limb) mixed ANCOVA, in which limb was the within-subjects factor and baseline scores were treated as a covariate. If the criteria for acute tolerance were met, the nature of the effect was examined with paired-samples t-tests for each dose condition using adjusted scores from the previous analyses to control for baseline differences in performance. For comparison of acute tolerance between high and low-dose conditions a 2 (group) × 2 (limb) ×2 (dose-size) mixed ANCOVA was conducted, with limb as the within-subjects factor and baseline scores of the entire sample treated as a covariate.

For subjective intoxication ratings, the requirement that BAC and intoxication were zero when testing commenced meant there was no need to control for baseline differences, accordingly a different analysis was conducted. Group differences on each limb were tested using independent samples t-tests. If an effect of alcohol was found on the ascending limb, and this effect was smaller on the descending limb, then an interaction between dose condition and limb was analysed with 2 (group) x 2 (limb) mixed-ANOVA, with limb as the within-subjects factor. If the criteria for acute tolerance was met, the nature of the effect was examined with paired-samples t-tests for each dose condition. For comparison of acute tolerance between dose conditions a 2 (group) × 2 (limb) ×2 (dose-size) mixed-ANOVA was conducted, with limb as the within-subjects factor.

Results

Blood Alcohol Concentrations

No detectable BAC was observed in baseline measures from either active-dose group, nor in any BAC measure from either placebo-control group once residual mouth alcohol from the placebo beverage had been eliminated. The analysis of BAC data was therefore restricted to that from the active dose-groups, post-beverage administration.

The low active-dose group reached a mean peak BAC of 0.059% (SD = .0054), and the mean peak BAC reached in the high active-dose group was 0.08 (SD = .0087). An independent samples t-

test confirmed the difference of 0.022% between groups was significant (t [52] = 11.17, p <0.001). Neither group differed significantly from the respective target BAC (low dose: t [26] = 1.25, p = .22, high dose: t [26] = 0.42, p = .68).

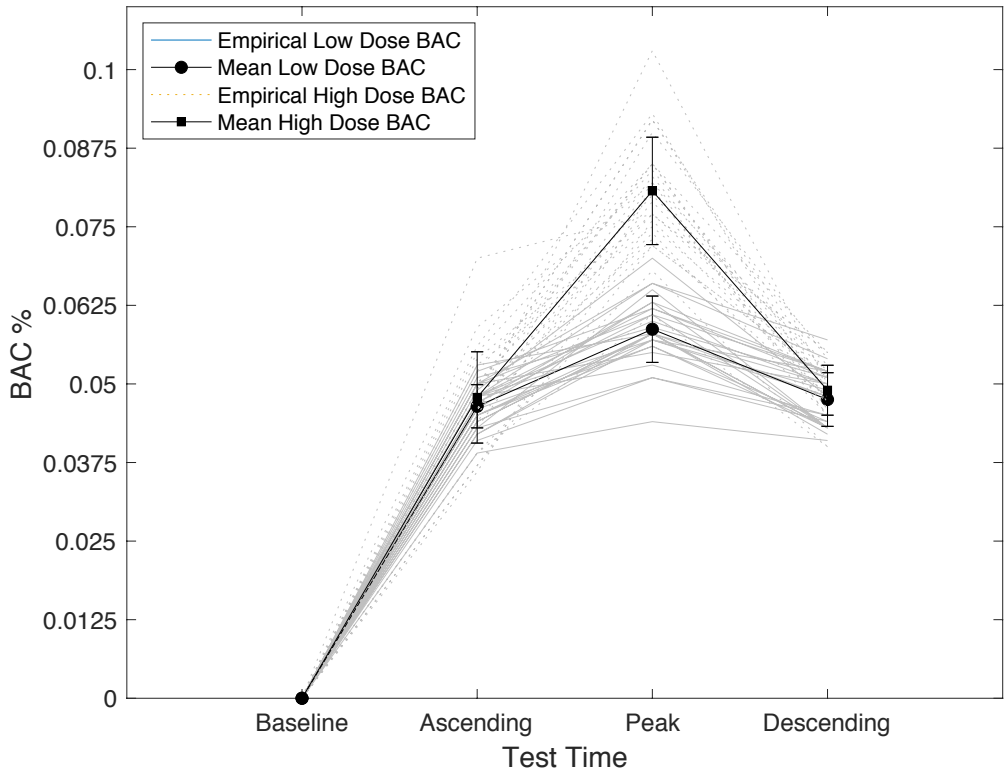


Figure 14: Means and error bars (±1 SD) for blood alcohol concentration (BAC) for both High and Low-active dose groups, together with individual participant BAC levels measured at baseline, on the ascending limb, at peak BAC. (Note: the times post dose that measures occurred varied between participants; see below)

Test-specific BACs on each limb for each participant were calculated by averaging the BAC from the commencement and completion of each test session. For the low active-dose group the mean test-specific BAC on the ascending limb was 0.046% (*SD* = 0.003), and on the descending limb 0.047% (*SD* = 0.004). Comparison of test-specific BAC's showed differences between limbs were not statistically significant (t [26] = 1.27, p =.21). In the high active-dose group the mean test-specific BAC on the ascending limb was 0.048% (*SD* = 0.007), and on the descending limb 0.049% (*SD* = 0.004). Comparison of test-specific BAC's showed that differences between limbs were not statistically significant (t [26] = 0.97, p =.34).

Independent samples t-tests comparing test specific BACs between groups found neither the ascending limb (t [52] = 0.86, p = .4) or descending limb (t [52] = 1.35, p = .18) test specific BACs

were significantly different between active-dose groups. The mean time (minutes post-consumption) of descending limb measures was statistically significant between high (M = 151.6, SD = 34.4) and low (M = 82.2, SD = 21.5) dose conditions (t [106] = 12.56, p < .001). As differences between limbs within dose conditions, and differences between dose conditions for each limb were not significantly different, changes in BAC during the dose were suitably controlled for to test for both a decrease in the dose-effect, and the effect of dose-size on changes in dose-effect. A reduction in the effect of alcohol from the ascending limb to the descending limb, could not be attributed to a decrease in BAC, nor could differences observed between dose sizes be attributed to differences in BAC at the time of testing.

Subjective intoxication

In both dose conditions, active-dose groups gave significantly higher ratings of peak intoxication (low dose; t [26] = 7.80, p < .001, high dose; t [26] = 6.67, p < .001). Figure 14 plots subjective ratings for each group on both limbs from both dose conditions.

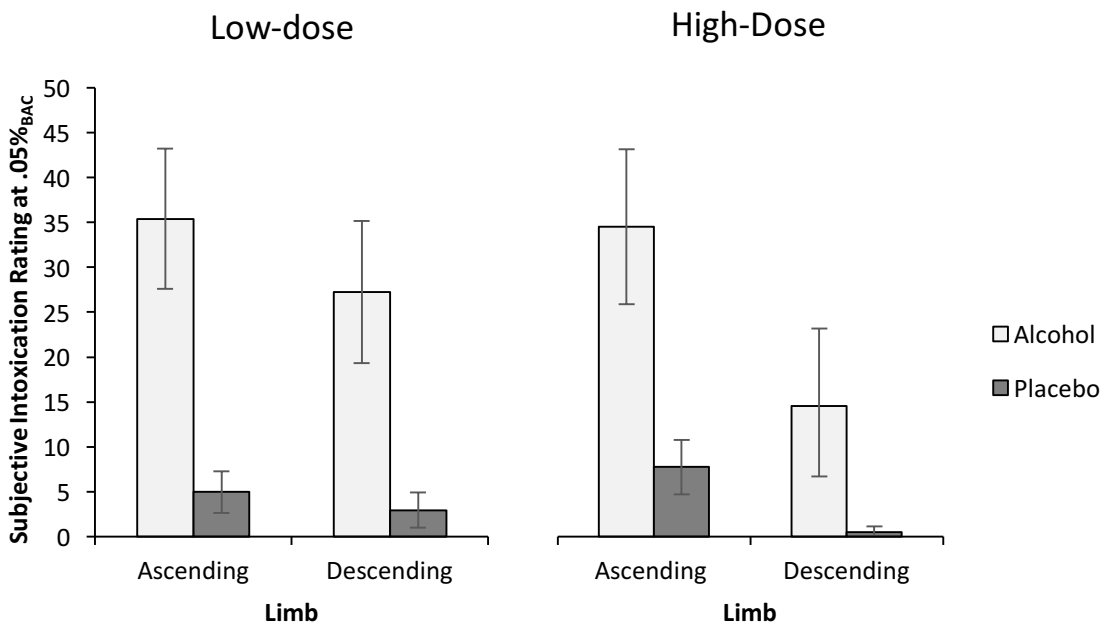


Figure 15. Mean ratings of subjective intoxication and error bars (+1 SEM) in dose and placebo groups on each limb

In the low-dose condition, ratings of subjective intoxication were significantly different between the active-dose and placebo group on both the ascending (t [52] = 7.68, p < .001, d = 2.09) and descending limb (t [52] = 6.10, p < .001, d = 1.66). Although the subjective effect of alcohol was

seen to be smaller on the descending limb, the group × limb interaction was not significant (F [1, 52] = 3.16, p = .081, η^2 = .049). Thus, an acute tolerance effect was not able to be confirmed. Bayesian analysis also indicated that the data was less probable under the alternative hypothesis than under the null (0.14 to 1).

In the high-dose condition, both groups gave higher ratings of subjective intoxication on the ascending limb than on the descending limb. On the ascending limb, an effect of alcohol was shown by the active-dose group giving higher ratings of subjective intoxication than the placebo group (t [52] = 6.02, p <.001, d = 1.64). Consistent with an acute tolerance effect, the effect of alcohol on subjective ratings was smaller on the descending limb (t [52] = 3.66, p = .001, d = 0.99). This decrease was confirmed by a statistically significant group × limb interaction, (F [1, 52] = 9.72, p = .003, η^2 = .091). In the high dose condition, there was also a significant main effect of limb on ratings of subjective intoxication (F [1, 52] = 44.55, p <.001, η^2 = 0.42), owing to an overall decrease from the ascending to descending limb. Follow-up analysis within the active-dose group found that the decrease in ratings between limbs was significant (t [26] = 5.23, p <.001), and substantial (d = 0.85).

Stop Signal Task

Reactive inhibition.

20% condition.

In the low dose condition (Figure 15), alcohol was found to have an effect on SSRT in the 20% condition. Comparisons showed that the active-dose group needed a significantly longer stop-signal delay than the placebo group on the ascending limb of the BAC curve (F [1, 51] = 5.93, p = .019, d = 0.56). Consistent with an acute tolerance effect, this alcohol effect was smaller on the descending limb (F [1, 51] = 1.37, p = .25, d = 0.13). The acute tolerance effect was not able to be confirmed however as the interaction between limb and group was not significant (F [1, 49] = 1.55, p = .22).

In the high dose condition (Figure 16) no effect of alcohol was found. On both limbs, performance in the active-dose group did not differ significantly from that of the placebo group (ascending limb; F [1, 49] = 2.07, p = .16, descending limb; F [1, 49] = 1.47, p = .23).

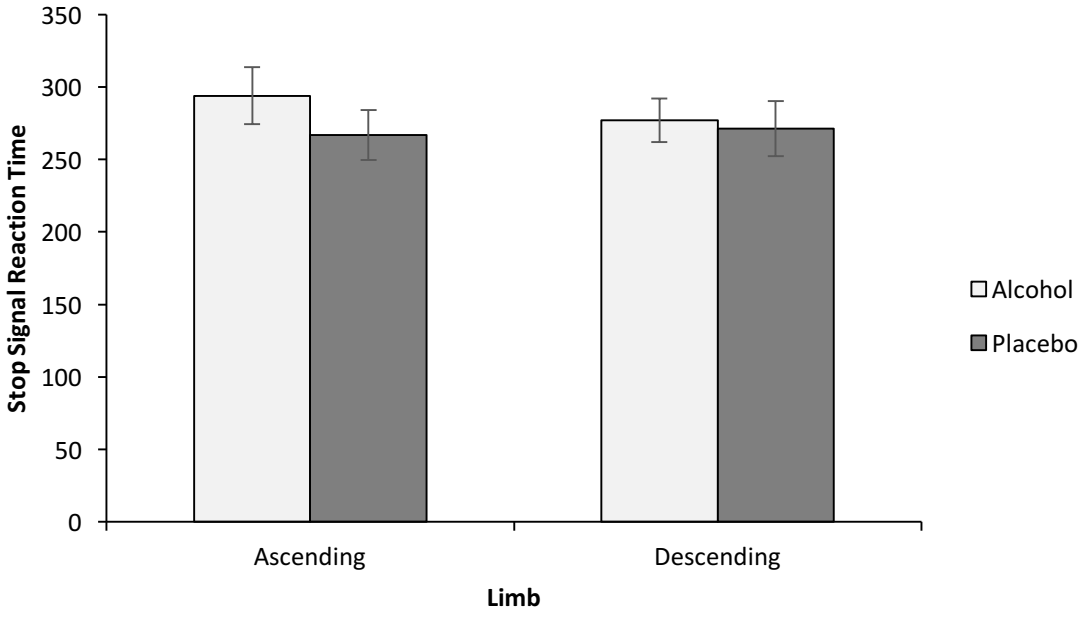


Figure 16. Adjusted Mean 20% SS probability trial Stop Signal Reaction Time and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the low dose condition

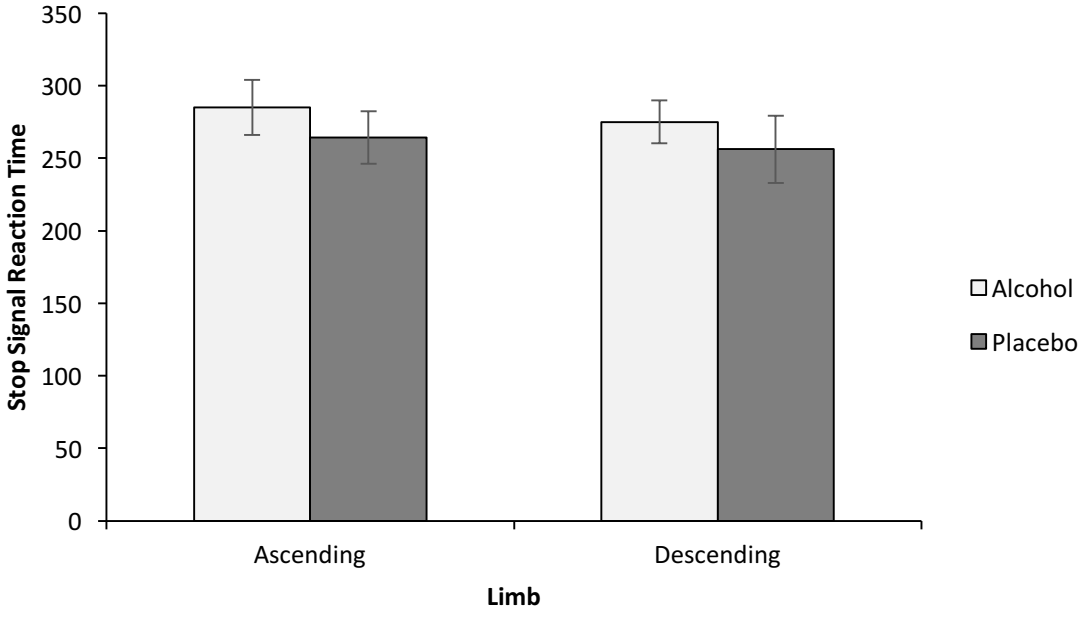


Figure 17. Adjusted Mean 20% SS probability trial Stop Signal Reaction Time and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the high dose condition

50% condition.

SSRT in the 50% condition did not show an effect of alcohol in either dose condition. The active-dose group did not differ from the placebo group on either limb, in either the low-dose condition (ascending limb; F [1, 51] = 0.70, p = .41, descending limb; F [1, 51] = 0.02, p = .88) or the high dose condition (ascending limb; F [1, 49] = 1.74, p = .19, descending limb; F [1, 49] = 0.72, p = .40).

Proactive Inhibition.

No measure of proactive inhibition showed an effect of alcohol in either dose condition as performance in the active-dose conditions did not differ significantly from the respective placebo group on either limb of the BAC curve (See Table 5).

Table 5
F-ratios and *p*-values for proactive inhibition measures

	SSRT difference		**PES**	
	Ascending limb	Descending limb	Ascending limb	Descending limb
Low	(F [1, 51] = 1.59, p = .21)	(F [1, 51] = 0.30, p = .58)	(F [1, 51] = 0.22, p = .64)	(F [1, 51] = 0.87, p = .36)
high	(F [1, 49] = 0.09, p = .78)	(F [1, 49] = 0.49, p = .48)	(F [1, 49] = 1.53, p = .22)	(F [1, 49] = 0.42, p = .52)

MCRT

Accuracy.

No effect of alcohol on accuracy was found in the low dose condition (Figure 17) as performance in the active-dose and placebo groups was not significantly different on either limb of the BAC curve (ascending limb; F [1, 53] = 0.15, p = .70, descending limb; F [1, 53] = 0.013, p = .91). An effect of alcohol on accuracy was found in the high-dose condition (Figure 18). On the ascending limb the active-dose group made more errors than the placebo group (F [1, 53] = 7.48, p = .009, d = 0.70). Consistent with an acute tolerance effect, the difference in performance was smaller on the descending

limb (F [1, 53] = 3.86, p = .055, d = 0.46). However, because the limb × group interaction was not significant (F [1, 51] = 0.29, p = .59), an acute tolerance effect was not confirmed

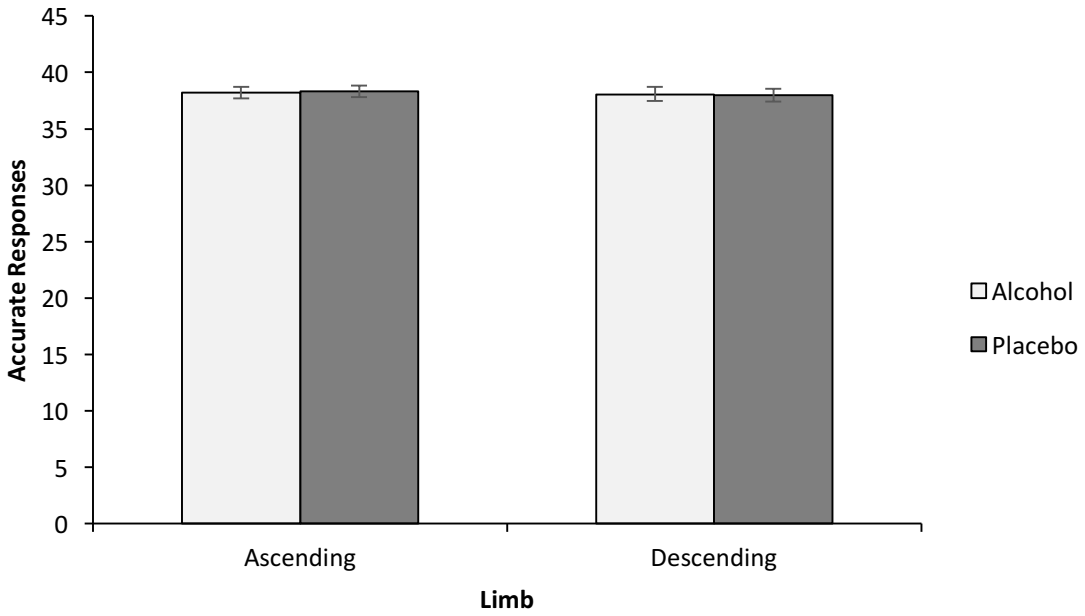


Figure 18. Adjusted Mean MCRT accuracy and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the low dose condition

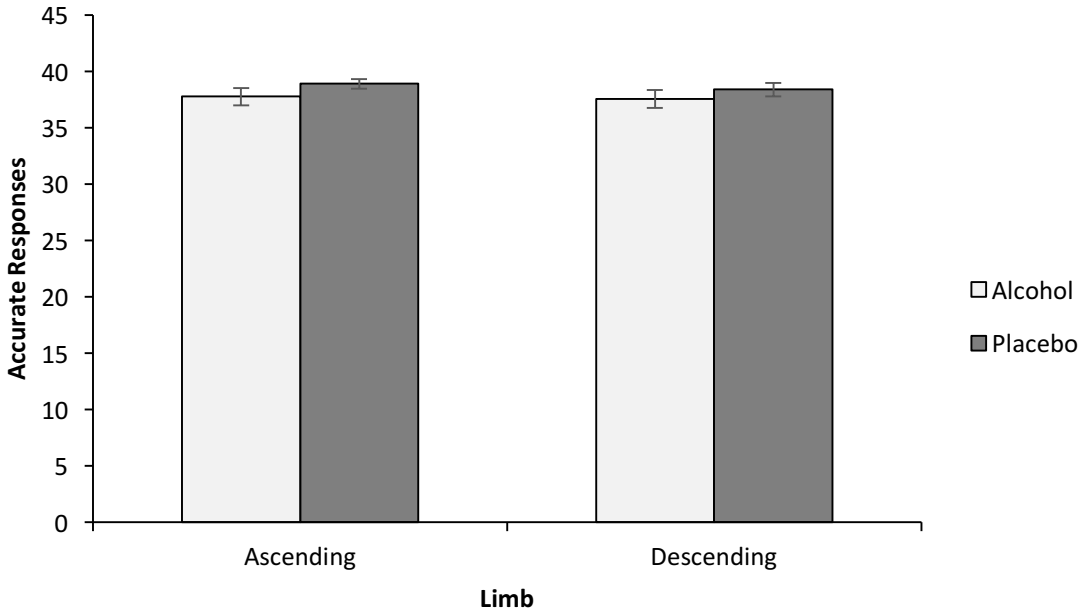


Figure 19.Adjusted Mean MCRT accuracy and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the high dose condition

Reaction Time.

Alcohol affected performance in reaction time in the low-dose condition (Figure 19). Compared to the placebo group, the low active-dose condition had longer reaction times on the ascending limb (F [1, 53] = 6.28, p = .015, d = 0.47). Consistent with an acute tolerance effect the size of the alcohol effect was smaller on the descending limb (F [1, 53] = 1.89, p = .17, d = 0.19). The interaction between limb and group was not significant (F [1, 51] = 2.63, p = .11), therefore the acute tolerance effect was unable to be confirmed. In the high-dose condition (Figure 20) an effect of alcohol on reaction time was not able to be found as groups did not differ significantly in performance on either the ascending (F [1, 53] = 0.004, p = .95) or descending limbs (F [1, 53] = 0.075, p = .79).

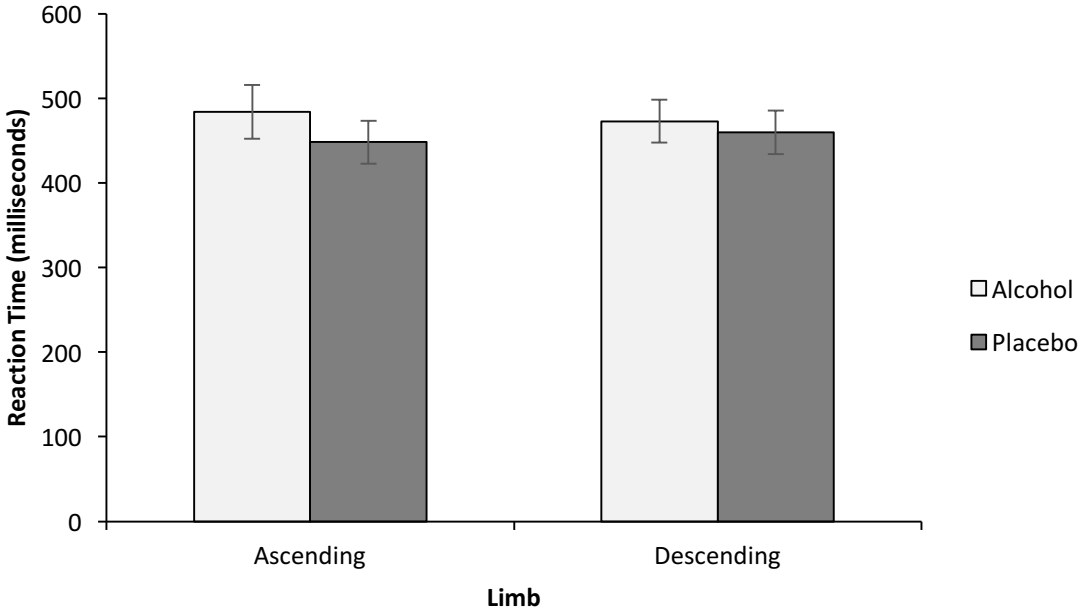


*Figure 20.*Adjusted Mean MCRT reaction times and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the low dose condition

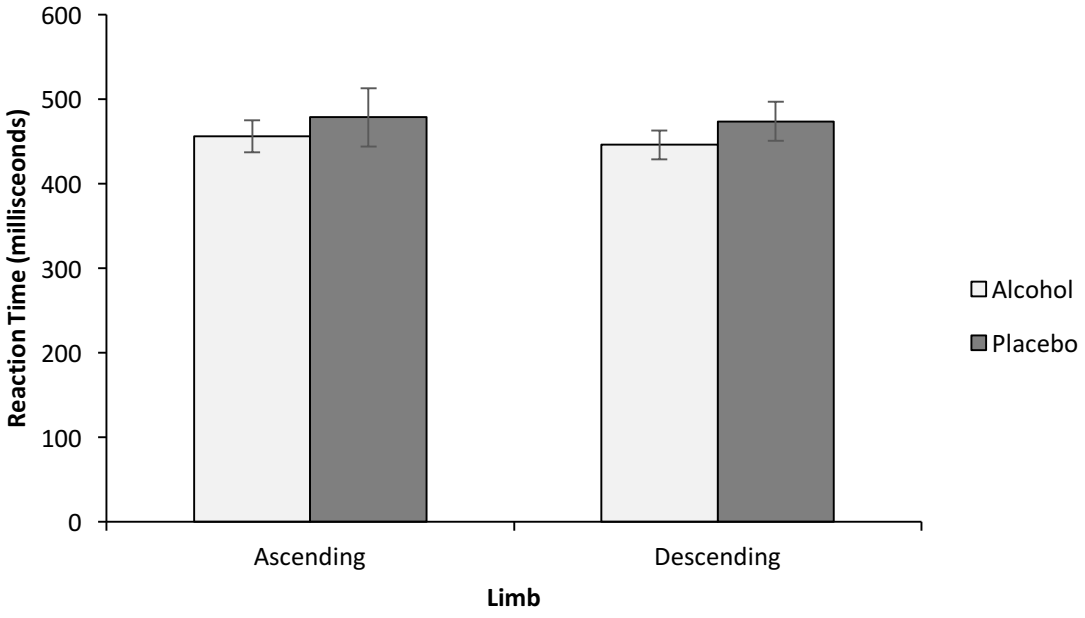


Figure 21. Adjusted Mean MCRT reaction time and error bars (+1 SEM) on each limb of the BAC curve for alcohol and placebo groups in the low dose condition.

Discussion

The aim of this study was to investigate whether acute tolerance could be observed in measures of subjective intoxication, response inhibition, and executive and psychomotor speed, and also, to examine the influence of dose size on the effect. In the low dose condition, alcohol impaired reactive inhibition in the Stop Signal Task (increased the stop signal delay time required to inhibit a response when the probability of a stop-signal occurring was .2) and response speed in the MCRT task on the ascending limb of the BAC curve. In the high dose condition, alcohol impaired accuracy of performance in the MCRT task on the ascending limb of the BAC curve. Consistent with a decrease in the dose-effect of alcohol, these effects of alcohol were no longer present in measures taken on the descending limb of the BAC curve. However, an acute tolerance effect was unable to be confirmed for any of these measures, as interactions between group and limb were not significant. In both dose conditions, alcohol was found to increase ratings in subjective intoxication relative to placebo. However, acute tolerance to subjective intoxication was only found in the high dose condition.

The present study used more rigorous criteria to test for acute tolerance than many previous examinations of the effect. Previous studies that have reported an acute tolerance effect after comparing the effect of alcohol between the limbs of the BAC curve have not always included a group

× limb interaction as a criterion for the effect. An absence of impairment on the descending limb after observing an impairment on the ascending limb has been used as evidence of a decrease in the dose-effect in previous studies that did not test the group x limb interaction (Mark T. Fillmore, Dixon, & Schweizer, 2000; Schweizer et al., 2006; Söderlund, Parker, Schwartz, & Tulving, 2005); by which standard the pattern of results for several objective measures in the current study would qualify as acute tolerance. While several measures that showed an effect of alcohol on the ascending limb were smaller when tested on the descending limb, the absence of a statistically significant limb × group interaction prohibits concluding that the decrease in the effect of alcohol seen in the active dose-condition was not equivalent to the change observed in the placebo group.

As the literature shows that acute tolerance is reliably demonstrated by measures of the subjective effects of alcohol, the finding of acute tolerance to subjective intoxication in the high dose condition was not unexpected. Even though the BAC of participants in the placebo groups remained at 0%, the consumption of the placebo beverage produced feelings of intoxication, which were seen to decrease between the ascending and descending limb measures. However, the decrease in ratings of intoxication seen in the high alcohol group was much larger. In the high alcohol group, the subjective intoxication produced at a BAC of approximately .05% decreased considerably in a period of two hours. The absence of a similar effect in the low dose condition was unexpected. Although this suggests that acute tolerance may only occur under higher doses, the effect has been previously found at similar BAC's under similar doses to those tested in the low dose condition (Cromer, Cromer, Maruff, & Snyder, 2010; Starkey & Charlton, 2014). An apparent difference between the two dose conditions is the time between measures. The average time of the descending limb measures in the low-dose condition was 70 minutes earlier than in the high-dose condition, which provided more time for a noticeable degree of acute tolerance to develop. The absence of affect for subjective could also potentially be due to a lack of statistical power. Our sample size was calculated to be adequately powered to detect effects comparable to those found in Comley & Dry (2020-b), which it was able to do under the higher dose but not the lesser one. Although a Bayesian analysis was consistent with the absence of the effect being more likely than an actual effect going undetected, we would still recommend further research into the effect on these measures with greater statistical power.

The differing pattern of the effect that alcohol had between groups in this study was particularly interesting, as BAC's were equivalent between groups at the time measures were taken. Despite

controlling for differences in BAC, all of the objective effects of alcohol seen in this study were unique to one dose-group. It has been previously suggested that rate of consumption affects the magnitude of alcohol effect (Viken, Rose, Morzorati, Christian, & Li, 2003), with faster consumption producing greater effects (Moskowitz & Burns, 1976). This hypothesis is supported by the reduced accuracy in the MCRT task being found uniquely in the high dose condition. However finding alcohol effects on measures only in the low alcohol group, which had a relatively slower consumption time, is not consistent with this notion. It may have been possible to use methods to control for rate of consumption, but such efforts would produce other confounds and have much lower ecological validity.

The impairment in Stop Signal Task performance seen in the low dose condition is consistent with previous findings of alcohol-induced impairment in response inhibition (Abroms et al., 2003; Dry et al., 2012). The finding in the current study is unique in that it is the first finding of an effect of alcohol specifically in reactive inhibition, while proactive inhibition showed no effect. This is interesting when taken alongside our findings of acute tolerance in subjective measures, given that reactive inhibition is presumably primarily a motor function, whereas proactive inhibition is largely cognitive. The absence of an acute tolerance effect in reactive inhibition seen in this study adds further support to the notion that response inhibition does not develop acute tolerance.

There are several limitations inherent in the Mellanby paradigm that the current study is hindered by. The direction that BAC is changing has been suggested to influence the effect of alcohol (Pohorecky, 1978). Although this study appropriately matched the time of measures on each limb to control for changes in BAC, comparing effects between limbs of the BAC curve necessitates the direction of the BAC change being different at the time of each measure (Rigter & Crabbe, 1980). The time between equivalent BAC's on each limb of the BAC curve is determined by the size of the dose. Thus the examination of the effect of the size of the dose using the Mellanby paradigm requires comparison between conditions with differing time elapsed between measures on each limb. A potential solution for these problems is the inclusion of additional paradigms for testing acute tolerance which do not compare the drug-effect between limbs of the BAC curve.

In Summary, this study tested for the acute tolerance in subjective intoxication, response inhibition and executive processing motor speed under two dose conditions. The effect was only found in subjective intoxication in the high dose condition. Alcohol was found to have an effect on several

measures, but these did not show a pattern of effect that could be confirmed as acute tolerance. The differing prevalence of findings of acute tolerance is alarming, as it suggests that people are likely to think they have recovered from the effects of alcohol while they remain impaired.

References

Abroms, B. D., Fillmore, M. T., & Marczinski, C. A. (2003). Alcohol-induced impairment of behavioral control: effects on the alteration and suppression of prepotent responses. *Journal of Studies on Alcohol, 64*(5), 687-695.

Beu, N. D., Burns, N. R., & Baetu, I. (In preparation). Remedial and probabilistic proactive inhibition: A conceptual distinction using a novel Stop-Signal Task.

Cash, C., Peacock, A., Barrington, H., Sinnett, N., & Bruno, R. (2015). Detecting impairment: Sensitive cognitive measures of dose-related acute alcohol intoxication. *Journal of Psychopharmacology, 29*(4), 436-446.

Comley, R. E., & Dry, M. J. (2020-a). Acute behavioral tolerance to alcohol. *Experimental and clinical psychopharmacology*, *28*(1), 112.

Comley, R. E., & Dry, M. J. (2020-b). Acute tolerance to alcohol-induced impairment in cognitive performance. *Experimental and Clinical Psychopharmacology*.

Cromer, J. R., Cromer, J. A., Maruff, P., & Snyder, P. J. (2010). Perception of alcohol intoxication shows acute tolerance while executive functions remain impaired. *Exp Clin Psychopharmacol, 18*(4), 329-339. doi: 10.1037/a0019591

Crow, K. E., & Batt, R. D. (1989). *Human metabolism of alcohol*. Boca Raton, Fla: CRC Press.

Dominy, N. J. (2004). Fruits, fingers, and fermentation: the sensory cues available to foraging primates. *Integrative and Comparative Biology, 44*(4), 295-303.

Dougherty, D. M., Bjork, J. M., & Bennett, R. H. (1998). Effects of alcohol on rotary pursuit performance: A gender comparison. *The Psychological Record, 48*(3), 393-405.

Dry, M. J., Burns, N. R., Nettelbeck, T., Farquharson, A. L., & White, J. M. (2012). Dose-related effects of alcohol on cognitive functioning. *PloS one, 7*(11), e50977.

Earleywine, M., & Erblich, J. (1996). A confirmed factor structure for the Biphasic Alcohol Effects Scale. *Experimental and Clinical Psychopharmacology, 4*(1), 107-113.

Fillmore, M. T., Dixon, M. J., & Schweizer, T. A. (2000). Alcohol affects processing of ignored stimuli in a negative priming paradigm. *Journal of Studies on Alcohol, 61*(4), 571-578.

Fillmore, M. T., Marczinski, C. A., & Bowman, A. M. (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *J Stud Alcohol, 66*(5), 663-672.

Fillmore, M. T., & Vogel-Sprott, M. (1998). Behavioral impairment under alcohol: cognitive and pharmacokinetic factors. *Alcoholism: Clinical and Experimental Research, 22*(7), 1476-1482.

Gengo, F. M., Gabos, C., Straley, C., & Manning, C. (1990). The Pharmacodynamics of Ethanol: Effects on Performance and Judgment. *The Journal of Clinical Pharmacology, 30*(8), 748-754. doi: 10.1002/j.1552-4604.1990.tb03638.x

Gopalakrishnan, S. (2012). A public health perspective of road traffic accidents. *Journal of family medicine and primary care, 1*(2), 144-150. doi: 10.4103/2249-4863.104987

Hames, G. (2014). *Alcohol in world history*: Routledge.

Hart, C. L., Ksir, C., & Ray, O. S. (2013). *Drugs, society & human behavior*: McGraw-Hill New York, NY.

Hiltunen, A. J. (1997). Acute alcohol tolerance in cognitive and psychomotor performance: influence of the alcohol dose and prior alcohol experience. *Alcohol, 14*(2), 125-130.

Kalant, H. (1996). Current state of knowledge about the mechanisms of alcohol tolerance. *Addiction Biology, 1*(2), 133-141. doi: 10.1080/1355621961000124756

Livesey, E. J., & Livesey, D. J. (2016). Validation of a Bayesian Adaptive Estimation Technique in the Stop-Signal Task. *PloS one, 11*(11), e0165525.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm.

Martin, C. S., & Moss, H. B. (1993). Measurement of acute tolerance to alcohol in human subjects. *Alcohol Clin Exp Res, 17*(2), 211-216.

McClelland, G. M., & Teplin, L. A. (2001). Alcohol Intoxication and Violent Crime: Implications for Public Health Policy. *The American Journal on Addictions, 10*(s1), s70-s85. doi: 10.1080/10550490150504155

McGovern, P. E. (2009). *Uncorking the past: the quest for wine, beer, and other alcoholic beverages*: Univ of California Press.

Mellanby, E. (1919). *Alcohol: Its absorption into and disappearance from the blood under different conditions* (Special Report Series No. 31). London, England: Medical Research Committee.

Meyer, J. S., & Quenzer, L. F. (2005). *Psychopharmacology: Drugs, the brain, and behavior*: Sinauer Associates.

Miller, M. A., & Fillmore, M. T. (2014). Protracted impairment of impulse control under an acute dose of alcohol: A time-course analysis. *Addictive Behaviors, 39*(11), 1589-1596. doi: 10.1016/j.addbeh.2013.10.035

Moskowitz, H., & Burns, M. (1976). Effects of rate of drinking on human performance. *Journal of Studies on Alcohol, 37*(5), 598-605.

Myers, R., & Veale, W. L. (1972). The determinants of alcohol preference in animals *The biology of alcoholism* (pp. 131-168): Springer.

National Health and Medical Research Council (2009). *Australian guidelines to reduce health risks from drinking alcohol*. Canberra: NHMRC

Nicholson, M. E., Wang, M., Airhihenbuwa, C. O., Mahoney, B. S., Christina, R., & Maney, D. W. (1992). Variability in behavioral impairment involved in the rising and falling BAC curve. *Journal of Studies on Alcohol, 53*(4), 349-356.

Pohorecky, L. (1978). Biphasic action of ethanol. *Biobehavioral Reviews, 1*(4), 231-240.

Rigter, H., & Crabbe, J. C. (1980). *Alcohol tolerance and dependence*. Amsterdam New York : New York: Elsevier/North-Holland Biomedical Press sole distributors for the U.S.A. and Canada, Elsevier/North Holland.

Saunders, J. B., Aasland, O. G., Babor, T. F., De la Fuente, J. R., & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88*(6), 791-804.

Schweizer, T. A., Jolicœur, P., Vogel-Sprott, M., & Dixon, M. J. (2004). Fast, but Error-Prone, Responses During Acute Alcohol Intoxication: Effects of Stimulus-Response Mapping Complexity. *Alcoholism: Clinical and Experimental Research, 28*(4), 643-649.

Schweizer, T. A., Vogel-Sprott, M., Danckert, J., Roy, E. A., Skakum, A., & Broderick, C. E. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacology, 31*(6), 1301-1309.

Söderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology, 182*(2), 305-317. doi: 10.1007/s00213-005-0096-2

Starkey, N. J., & Charlton, S. G. (2014). The effects of moderate alcohol concentrations on driving and cognitive performance during ascending and descending blood alcohol concentrations. *Hum Psychopharmacol, 29*(4), 370-383. doi: 10.1002/hup.2415

Streufert, S., Pogash, R. M., Roache, J., Gingrich, D., Landis, R., Severs, W., . . . Kantner, A. (1992). Effects of alcohol intoxication on risk taking, strategy, and error rate in visuomotor performance. *Journal of Applied Psychology, 77*(4), 515-524.

Tupler, L., Hege, S., & Ellinwood, E. (1995). Alcohol pharmacodynamics in young-elderly adults contrasted with young and middle-aged subjects. *Psychopharmacology, 118*(4), 460-470.

Viken, R. J., Rose, R. J., Morzorati, S. L., Christian, J. C., & Li, T.-K. (2003). Subjective intoxication in response to alcohol challenge: Heritability and covariation with personality, breath alcohol level, and drinking history. *Alcoholism: Clinical and Experimental Research, 27*(5), 795-803.

Vogel-Sprott, M., & Sdao-Jarvie, K. (1989). Learning alcohol tolerance: the contribution of response expectancies. *Psychopharmacology, 98*(3), 289-296. doi: 10.1007/BF00451677

Watson, P. E., Watson, I. D., & Batt, R. D. (1981). Prediction of blood alcohol concentrations in human subjects. Updating the Widmark Equation. *Journal of Studies on Alcohol, 42*(7), 547-556.

Weafer, J., & Fillmore, M. T. (2012). Comparison of alcohol impairment of behavioral and attentional inhibition. *Drug and Alcohol Dependence, 126*(1), 176-182.

World Health Organization (2014). *Global status report on alcohol and health*

Zhang, F., & Iwaki, S. (2019). Common neural network for different functions: an investigation of proactive and reactive inhibition. *Frontiers in Behavioral Neuroscience, 13*, 124.

Statement of Authorship

Title of Paper	Acute tolerance to subjective intoxication from alcohol
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Under review at 'Alcohol'

Principal Author

Name of Principal Author (Candidate)	Ross Edward Comley		
Contribution to the Paper	Experimental design, data collection, analysis, and interpretation, drafting of manuscript		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19/10/2020

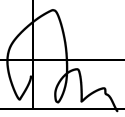
Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Matthew Dry		
Contribution to the Paper	General guidance as supervisor		
Signature		Date	20-10-20

3.4 Manuscript: Acute Tolerance to Subjective Intoxication From Alcohol

Acute tolerance to subjective intoxication from alcohol

R. Edward Comley

Dr Matthew J. Dry

Abstract

Acute tolerance is a rapid decrease in the dose-effect of alcohol occurring within the duration of a single dose. Numerous methods of examining changes in the dose-effect have been used previously to test for acute tolerance, with each having a unique rationale for determining if the effect has occurred, as well as specific advantages and limitations. This study tested for acute tolerance to the subjective intoxication from a single dose of alcohol using three different paradigms: the Mellanby paradigm, the peak-comparison paradigm, and the rate of recovery paradigm. The Mellanby paradigm compares drug-effect from two time points during a dose with equivalent BAC's (blood alcohol concentrations). The peak-comparison paradigm compares the times when BAC and drug-effect reach their peak. The rate of recovery paradigm examines differences in the rate that BAC and drug-effect decrease after reaching their peak value. One hundred and eight participants were allocated to one of four groups, either a high or low dose condition, and either an active dose or placebo group. Doses were calculated to produce a peak BAC of .08% in the high active dose group, and .06% in the low active dose group. After consuming the dose, BAC and ratings of subjective intoxication were repeatedly taken throughout the duration of the dose. In all three paradigms, an acute tolerance effect was observed in the high dose condition, but not in the low dose condition. The findings suggest that acute tolerance to subjective intoxication may be influenced by the size of the dose, and highlight the advantages of using multiple paradigms when examining the effect.

Keywords: alcohol; acute tolerance; subjective intoxication; Mellanby effect; peak comparison; rate of recovery

Introduction

Acute tolerance is a rapid decrease in the dose-effect of alcohol, occurring within the duration of a single exposure to the drug (Hendershot et al., 2015; Martin & Moss, 1993). The *dose-effect*, is the strength of the effect produced by the drug relative to the size of the dose. Unlike chronic tolerance which is acquired over accumulative exposures and hence observed across doses, acute tolerance is seen on a much shorter time-scale, e.g. within 60-90 minutes (Kalant, 1996). The appropriate measure of dose-size at a time during a dose is the *blood alcohol concentration* (BAC). When acute tolerance develops, the effect of alcohol at a given BAC is seen to diminish, requiring a higher BAC to reinstate the initial strength (Fillmore, Marczinski, & Bowman, 2005). As this effect occurs immediately when alcohol is consumed, its rapid nature has implications for real-world drinking behaviour (Banks, Vogler, & Weissbach, 1979; Earleywine & Erblich, 1996).

Studies examining acute tolerance have frequently found differences between subjective and objective behavioural measures used to gauge the drug-effect. Although acute tolerance has been found in an array of objective measures like simple reaction time, motor coordination and executive functions, others such as response inhibition and simulated driving, appear to be resistant to the effect (Schweizer, Jolicœur, Vogel-Sprott, & Dixon, 2004). In contrast, subjective measures, which measure the perceived effects of alcohol using self-rating scales, reliably show acute tolerance (Comley & Dry, 2020-a). The ecological significance of the disparity in acute tolerance between subjective and objective measures is evident in the context of intoxicated driving. In which it is likely a person would perceive they had recovered from the impairing effects of alcohol while their BAC remained elevated, thus increasing the likelihood of deciding to drive while still intoxicated and impaired.

The subjective experience of intoxication that alcohol produces is a primary reason why people consume it. Thus, acute tolerance to the subjective effects of alcohol can also be seen as a likely contributor to excess consumption, as a decrease in effect relative to BAC would necessitate reaching higher BAC to experience a given magnitude of effect (Aston & Liguori, 2013). Accounting for acute tolerance as a factor influencing drinking behaviour is not a strategy widely promoted in responsible drinking campaigns.

The BAC produced from a single dose of alcohol follows a reliable two-limbed (ascending, descending) curve, initially rising quickly from baseline to peak, and then declining at a slower rate

back to baseline (Watson, Watson, & Batt, 1981). Changes in BAC reliably change the strength of the psychoactive effects of alcohol. Therefore, changes in BAC must be controlled for, in order to observe a decrease in the drug-effect relative to the BAC (Rigter & Crabbe, 1980). The most common method for controlling for changes in BAC has been to compare the drug-effect between earlier and later times during a dose when BAC is equivalent, by taking measures at certain times on each limb of the BAC curve (see Figure 21). If acute tolerance occurs the effect of alcohol will be weaker on the descending limb than on the ascending limb. This method is attributed to Mellanby (1919) who first reported the effect after observing it in a small sample of dogs. Acute tolerance to the subjective effects of alcohol has frequently been observed using the Mellanby paradigm.

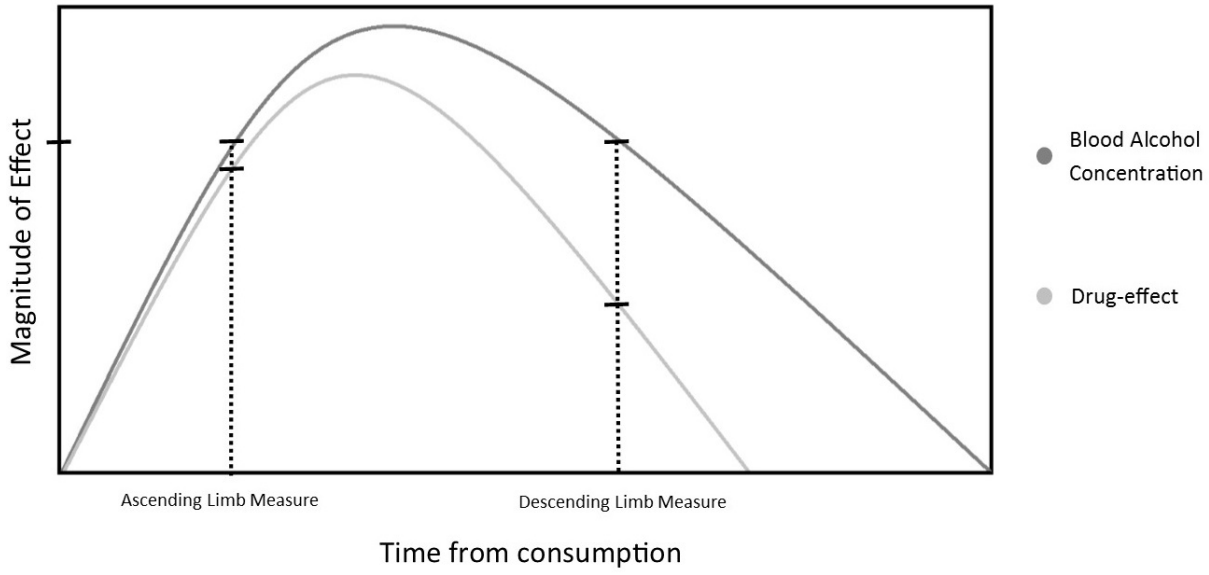


Figure 22. Limb comparison for BAC and Drug-effect showing a decrease in drug-effect between limbs at equivalent BAC's. Adapted from Comley & Dry (2020-a).

Other methods of examining changes in the dose-effect have been used to test for acute tolerance. Each has a unique rationale for determining if acute tolerance has been observed from the data it provides, and each has certain advantages and limitations. An inherent limitation of comparing the drug-effect between limbs of the BAC curve is that the direction of BAC change is unable to be controlled for because comparisons between equal BAC's during a single dose necessitate measures being taken when BAC is both increasing and decreasing (Rigter & Crabbe, 1980). Thus, decreases dependent on the direction of BAC change are unable to be distinguished from those that are not.

The simpler *peak comparison* paradigm involves testing for acute tolerance by comparing the times when BAC and drug-effect reach their peak. If acute tolerance occurs, then the drug-effect will peak and begin to decrease earlier than BAC (Ellinwood, Linnoila, Easler, & Molter, 1981). This asymmetry results from the dose-effect decreasing faster than the BAC is increasing (Figure 22). This paradigm has only been used to examine acute tolerance to subjective effects in one previous study (Radlow & Hurst, 1985), which found the peak subjective intoxication from a dose of 1.0g/kg occurred 24 minutes earlier than peak BAC. Accurate estimates of the time peak values occur for each measure require more frequent measures than the Mellanby paradigm. However, because it does not compare the drug-effect between limbs it is not influenced by the direction of BAC change.

Another method, the *rate of recovery* paradigm, compares the speed that the drug-effect and BAC decrease after peaking (Figure 23). If the dose-effect is decreasing, the drug-effect will decrease at a faster rate than BAC (Vogel-Sprott & Fillmore, 1993; Radlow, 1994; Post, Tavano, & Maddock, 1998). Like the peak comparison paradigm, it requires frequent measures and is not affected by the direction of BAC change. A specific advantage is that it can quantify the rate that acute tolerance develops by comparing the difference between BAC and drug-effect over time. To our knowledge, the rate of recovery paradigm has only been used to examine acute tolerance in subjective intoxication in one prior study (Martin & Moss, 1993), which compared acute tolerance findings between the rate of recovery paradigm, the Mellanby paradigm, and an area under the curve measure. Martin and Moss (1993) reported that all three paradigms showed acute tolerance with a majority of subjects data, but also noted that the rate of recovery paradigm did not correlate with the either of the other two paradigms; which is indicative of differences between the limbs of ther BAC curve in processes other than acute tolerance.

The aim of this study was to examine acute tolerance in subjective intoxication using the three aforementioned paradigms, under two different dose sizes. Despite a large body of literature reliably demonstrating acute tolerance, there are still numerous gaps in our knowledge of the effect. A major limitation in our current understanding of acute tolerance is how the effect varies with the size of the dose. Several studies have previously attempted to compare acute tolerance between different dose sizes (Earleywine & Erblich, 1996; Gengo, Gabos, Straley, & Manning, 1990; Nicholson et al., 1992; Starkey & Charlton, 2014; Streufert et al., 1992; Tupler, Hege, & Ellinwood, 1995). However, these

studies have been limited to the Mellanby paradigm and the findings are largely conflicting. How acute tolerance is influenced by the size of the dose is still unclear, and it was intended that using multiple paradigms would provide a more robust examination.

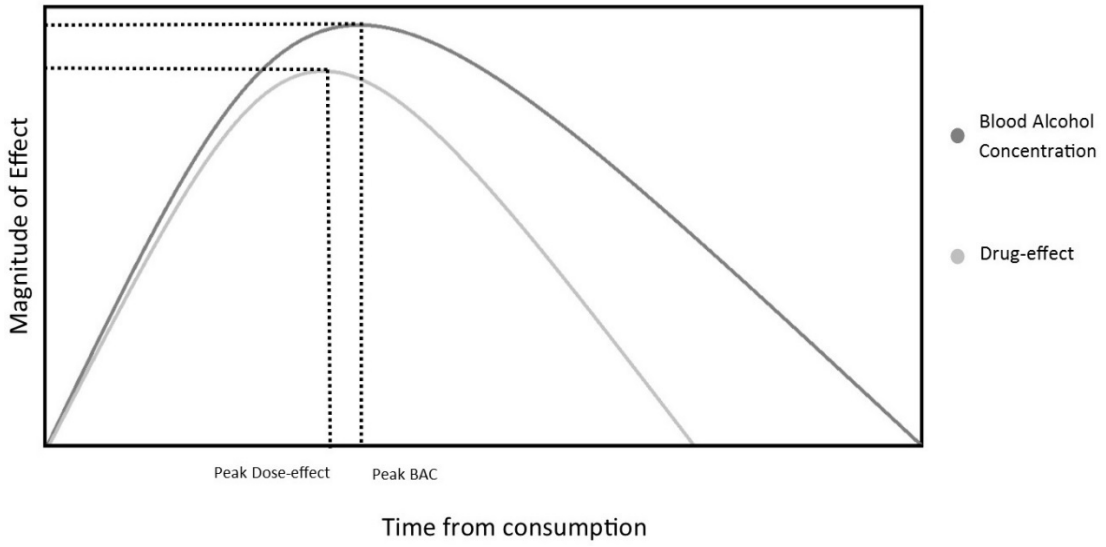


Figure 23. BAC vs Drug-effect during the time course of a single dose showing different peak times. Adapted from Comley & Dry (2020-a).

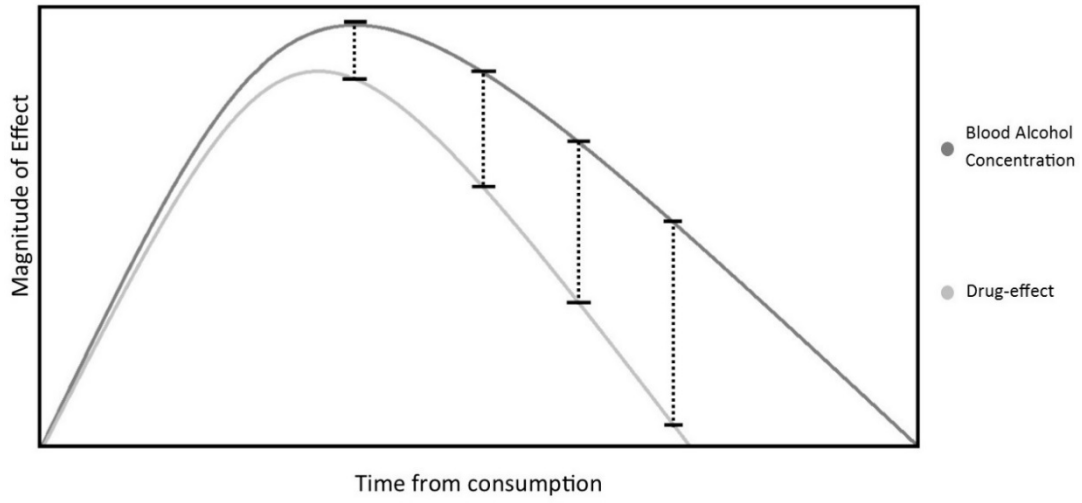


Figure 24. BAC vs Drug-effect during the time course of a single dose showing a comparison of rates of recovery. Adapted from Comley & Dry (2020-a).

Method

Participants

Approval to conduct this study was granted by the University of Adelaide's Human Research Ethics Committee. An online scheduling system was used to conduct the recruitment of participants. Using the Mellanby paradigm, to find an effect size similar to the acute tolerance previously found in subjective intoxication (F = 8.71; Comley & Dry, 2020-b) with power at 0.95 and alpha 0.05, our sample size needed to be N = 4 in each dose condition. One hundred and eight, First-year university students (59 women), aged 18-33 (M = 19.7, SD = 2.78) participated in return for course credit.

Each participant's eligibility to participate was subject to the following criteria:

(xi) aged 18–45 years,

(xii) not currently pregnant or lactating

(xiii) no major medical or psychiatric conditions

(xiv) no uncorrected visual disorders

(xv) no dependence on any substance (excluding nicotine)

(xvi) fluent in English

(xvii) no history of alcohol-related problems

(xviii) not taking medication having a stimulative or sedative action, and

(xix) had consumed at least three alcoholic beverages on at least one occasion in the past month.

(xx) had not consumed alcohol or other drugs (except nicotine) in the previous 24 hours

The range of participant age was limited to ensure that participants were of legal drinking age, and were unlikely to be affected in their task performance by age-related cognitive decline. The inclusion of Criterion (ix) was to ensure that participants had some familiarity with the alcohol doses being given. Participants were also excluded if they reported risky drinking behaviour. This was assessed using the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT is a 10-item questionnaire reporting the occurrence and severity of alcohol-related problems during the last twelve months (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). Participants who scored 15 or higher were excluded, but no participant reached this criterion level.

Measures

Subjective Intoxication.

A visual analogue scale (VAS) was used to measure the subjective effects of alcohol. A 100mm long black line with the label "level of felt intoxication" was printed on a length of paper, with each end anchored left to right from "not at all" to "very much". Participants were instructed to mark a vertical line through the scale at the point which equated to their current level of intoxication. Ratings were recorded as mm from baseline.

Breathalyzer.

BAC was measured from breath samples with a standardized Breathalyzer (Lion brand model 500P). Note that readings are reported as BAC and not Breath Alcohol Concentration (BrAC), as the Breathalyzer calculates BrAC to give readings as BAC.

Demographics.

A self-report questionnaire was used to record general demographic information for each participant. Responses regarding gender and body weight were used to calculate alcohol doses. A digital scale was used to measure participants' body weight.

Procedure

Immediately after scheduling their participation, participants received instructions to eat a normal breakfast then fast for four hours prior to their session. They were also instructed to refrain from consuming alcohol or other drugs (except nicotine), for 24 hours prior to their participation. Participants were briefed on the procedure and the effects of alcohol upon arriving at the laboratory at approximately 12 pm, then gave informed consent. After participants completed the demographic questionnaire and the AUDIT, a baseline measure of BAC was taken to ensure that participants began the procedure with a BAC of 0%. The VAS was then explained, and a baseline measure of 0mm was recorded.

Participants were randomly pre-allocated to one of four groups, either a high or low dose condition, and either an active dose or placebo dose group. Those in the alcohol group were given alcohol in the form of vodka (40% alcohol v/v) mixed with orange juice in a 2:9 mix, divided equally into three cups. Participants in the placebo-control groups received an equal volume of juice. To give the impression that the placebo beverages contained a dose of alcohol, three ml of vodka (less than effective dose) was floated on the surface of the drink and coated on the rim of the cup. The Widmark

equation was used to calculate dose volumes for each participant in the alcohol groups. Doses were calculated to produce a peak BAC of .06% in the low dose condition, and .08% in the high dose condition. All participants were told that the beverages given may or may not contain any alcohol. The consumption period lasted twelve minutes, with each cup being given at four-minute intervals and participants instructed to drink each at a steady pace over four minutes. After all three beverages had been drunk participants were given spring water to rinse their mouths and sip.

BAC measures were taken at 20, 35, 45 minutes and every 15 minutes thereafter. Subjective intoxication ratings were taken with each BAC measure. Each participant in the placebo-control group was anchored to a participant in the corresponding active dose group and tested at equivalent times. Light snacks were served to participants after the descending limb trials. Participants remained until BAC<0.01%, after which time they were debriefed and permitted to leave.

Data Analysis

Analyses were conducted using IBM SPSS Statistics 22 (IBM Inc., Armonk, NY, US).

Mellanby Paradigm.

To test for an effect of alcohol on each limb, independent samples t-tests were used to compare differences in subjective intoxication ratings between active dose and placebo groups. If an effect of alcohol was found on the ascending limb, and this effect was smaller on the descending limb, then an interaction between dose condition and limb was analysed with 2 (group) x 2 (limb) mixed-ANOVA, with limb as the within-subjects factor. If the criteria for acute tolerance was met, the nature of the effect was examined with paired-samples t-tests for each dose condition. For comparison of acute tolerance between dose conditions a 2 (group) × 2 (limb) ×2 (dose-size) mixed-ANOVA was conducted, with limb as the within-subjects factor.

Peak Comparison Paradigm.

Data from placebo groups was not needed to be included in the examination of peak BAC and Peak intoxication comparisons, analyses were therefore limited to active dose groups. Mean time of peak BAC and Mean time of peak subjective intoxication ratings were compared using paired samples t-test. The effect of dose size was examined using a 2 (peak-BAC vs Peak-Subjective Intoxication) ×2 (dose-size) mixed-ANOVA with peak measures as the within-subjects factor.

Rates of Recovery Paradigm.

Each participant's BAC and subjective intoxication ratings were converted to a percentage of that participant's maximum. Correlations between each measure and time in minutes from maximum were conducted to ascertain there was a significant linear relationship. If so, two linear regressions were performed with time from maximum as the independent variable and subjective intoxication ratings and BAC as the dependent variables to calculate the slope function (beta coefficients) for each variable as a measure of the rate each was recovering as %/minute. The effect of dose size was examined by comparing the difference in slope functions from each dose condition.

Results

Blood Alcohol Concentration

Analysis of BAC data was limited to that from the active dose-groups, as no detectable BAC was found in any measure from either placebo group once residual mouth alcohol had been eliminated. Mean peak BAC reached by the low active-dose group was 0.059% (*SD* = .0054) and 0.081% (*SD* = .0087) in the high active dose group. Neither group differed significantly from the respective target BAC (low dose; t [26] = 1.25, p = .22, high dose; t [26] = 0.42, p = .68).

For the Mellanby paradigm, each participant's specific measures for each limb were calculated by averaging the BAC and VAS from beginning and end of a 15-minute interval when the BAC was approx.. .05%. The mean test-specific BACs for the low active-dose group were 0.046% (SD = 0.0035) on the ascending limb, 0.047% (SD = 0.0043) on the descending limb, and were appropriately matched (t [26] = 1.27, p = .21). In the high active-dose group the mean test-specific BACs were 0.048% (SD = 0.0074) on the ascending limb, and 0.049% (SD = 0.0041) on the descending limb, and were also appropriately matched (t [26] = 0.97, p = .34). Comparison of test specific BACs between groups on each limb using independent sample t-tests showed that neither the ascending limb (t [52] = 0.86, p = .4) or descending limb (t [52] = 1.35, p = .18) test specific BACs were significantly different between active-dose groups. A decrease in dose-effect between limbs within dose-conditions and the effect of dose-size on such changes were able to be examined through limb and group comparisons, as differences between limbs within dose conditions, and differences between dose conditions on each limb were not significantly different. A reduction in the effect of alcohol from the ascending limb to the descending limb, could not be attributed to a decrease in BAC, nor could differences observed between dose sizes be attributed to differences in BAC at the time of testing. However, the mean time

of descending limb measures was statistically significant between high and low dose conditions (low dose: M = 82.2 minutes, SD =21.5; high dose: M = 151.6 minutes, SD = 34.4; t [106] = 12.561, p < .001).

Subjective Intoxication

Compared to the placebo groups, active dose groups in both dose conditions gave significantly higher ratings of peak intoxication (low dose; t [26] = 7.804, p < .001; high dose; t [26] = 6.671, p < .001).

Mellanby Analysis.

Figure 24. plots subjective ratings for each group on both limbs from both dose conditions.

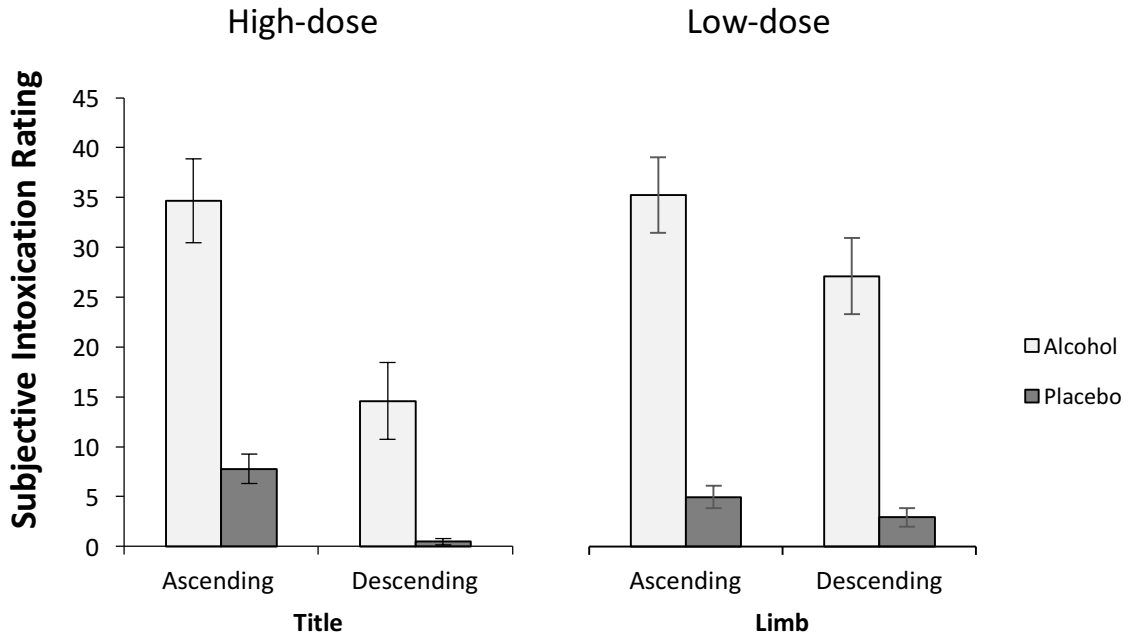


Figure 25. Mean ratings of subjective intoxication and error bars (+1 SEM) for active dose and placebo groups on each limb

High Dose.

In the high-dose condition, subjective intoxication ratings given by both groups were higher on the ascending limb, however the alcohol group gave higher ratings of subjective intoxication than the placebo group, on both limbs, (ascending, t [52] = 6.02, p < .001, d = 1.64; descending, t [52] = 3.66, p = .001, d = 1.0). Consistent with an acute tolerance effect the effect of alcohol on subjective intoxication was smaller on the descending limb. This decrease was confirmed by a statistically significant group × limb interaction, (F [1, 52] = 9.72, p = .003, η^2 = .091). There was also a significant

main effect of limb in the high dose condition owing to an overall decrease from the ascending to descending limb (F [1, 52] = 44.55, p < .001, η^2 = 0.42). Follow-up analysis found that the decrease in ratings between limbs in the alcohol group was significant (t [26] = 5.23, p < .001), and substantial (d = 0.96).

Low Dose.

In the low-dose condition, the active dose group gave significantly higher subjective intoxication ratings than the placebo group on both the ascending (t [52] = 7.69, p < .001, d = 2.09) and descending limb (t [52] = 6.10, p < .001, d = 1.66). Although difference between groups was smaller on the descending limb, an acute tolerance effect was not able to be confirmed, because the group × limb interaction was found to not be significant (F [1, 52] = 3.16, p = .081, η^2 = 0.05). Bayes factor also indicated that the data was less probable under the alternative hypothesis than under the null (0.14 to 1).

Peak Comparison Analysis.

High Dose.

In the high dose condition, peak BAC occurred at a mean time of 77.2 minutes (SD = 17.5). Consistent with an acute tolerance effect, peak ratings of subjective intoxication occurred at a mean time of 48.8 minutes (SD = 20.3). The acute tolerance effect was confirmed by paired samples t-test (t [26] = 6.12, p < .001).

Low Dose.

In the low dose condition, peak BAC occurred at a mean time of 55.6 minutes (SD = 14.3). Consistent with an acute tolerance effect, peak ratings of subjective intoxication occurred earlier than peak BAC (M = 46.6, SD = 23.4). However, paired-samples t-test showed that the difference in times of peak BAC and peak rating was not significant (t [26] = 1.73, p = .095, BF_{10} = 0.76).

Dose Comparison.

As differences between peak BAC and peak subjective intoxication ratings approached significance and Bayesian analysis provided some support for an effect in the low dose condition, an examination of the effect of dose size was conducted (Figure 25). There was a significant interaction between dose condition and peak times (F [1, 52] = 7.80, p = .007, η^2 = .13). Follow up pairwise comparisons showed that although there was a difference in peak BAC times between dose conditions as expected (t [52] = 4.98, p < .001), there was no difference in the time of peak intoxication ratings

between dose conditions (t [52] = 0.37, p = .71). This would indicate that there was faster recovery from the subjective effects under the higher dose, to the extent that the larger dose produced no greater duration of increasing effect than the smaller dose.

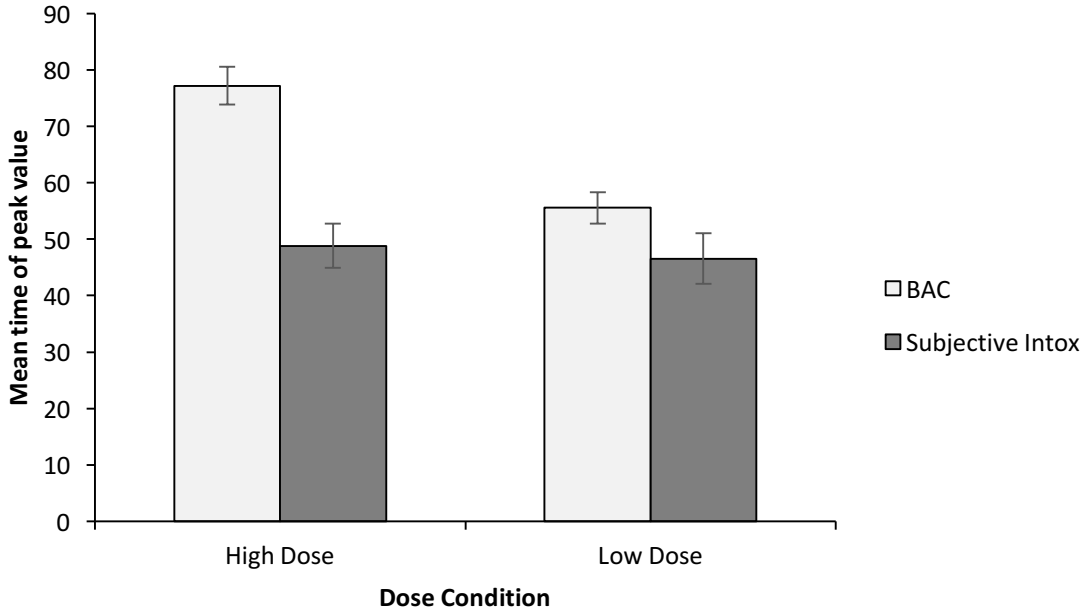


Figure 26. Mean times of peak BAC and peak subjective intoxication rating in both dose-conditions (error bars = +1 SEM)

Rates of Recovery Analysis.

High Dose.

In the high dose condition, time after peak was significantly correlated with both BAC (r [34] = -.89, p < .001) and Subjective intoxication ratings (r [285] = -.77, p < .001). Linear regression between Time after peak and BAC had a slope of b = -0.004. The slope of the regression line between time after peak and subjective intoxication ratings was b = -0.005. In the high dose condition, BAC recovered at a rate of .4% per minute, while subjective intoxication ratings recovered at 0.5% per minute, meaning that subjective intoxication ratings were recovering 25% faster than BAC.

Low Dose.

In the low dose condition time after peak was significantly correlated with both BAC (r [248] = -.886, p < .001) and Subjective intoxication ratings (r [224] = -.709, p < .001). Linear regression between time after peak and BAC had a slope of b = -0.005. The slope of the regression line between

time after peak and subjective intoxication ratings was also b = -0.005. In the low dose condition, both BAC and subjective intoxication ratings recovered at the same rate of 0.5% per minute.

Discussion

This study aimed to compare acute tolerance to subjective intoxication between two dose sizes using three different research paradigms. In the Mellanby paradigm, the drug-effect at a BAC of approximately .047% was compared between each limb of the BAC curve in each dose condition. In both dose conditions alcohol increased ratings of subjective intoxication relative to placebo on both limbs of the BAC curve, and consistent with an acute tolerance effect, this effect of alcohol was seen to be less on the descending limb despite no significant change in BAC. However, unexpectedly, the acute tolerance effect was only able to be confirmed in the high dose condition. Likewise, for the peak comparison analysis, examination of peak BAC and peak drug-effect only showed acute tolerance in the high-dose condition. In the high dose condition, peak subjective intoxication occurred 28 minutes earlier than peak BAC. Comparison of peak times between dose-conditions showed that although peak BAC occurred later in the high dose condition, there was no difference in the time peak subjective intoxication occurred between dose sizes. The rate of recovery paradigm was able to determine that in the low dose condition BAC and drug-effect both recovered at an equivalent rate of 0.5% of maximum per minute, which suggests that the dose-effect in the low dose condition remained stable during the dose, consistent with the findings of the other two paradigms which did not show acute tolerance. In the high dose condition, indicative of a decreasing dose-effect, subjective intoxication recovered at a rate 25% faster than BAC. As all three paradigms showed the same pattern between dose conditions, these results suggest that acute tolerance is more likely to occur under higher doses.

The finding of a decrease between limbs only in a higher dose condition is consistent with the findings of Nicholson et al. (1992) and Streufert et al. (1992). But this was the first study to find such a pattern of effect between dose sizes in subjective intoxication. The absence of acute tolerance in the low dose condition is surprising as the effect has been demonstrated previously under similar doses. The criterion of a significant group × limb interaction was included in this study to test that the observed decrease between limbs was not a type-1 error. Several previous studies have not included an interaction as necessary to show acute tolerance (Mark T. Fillmore, Dixon, & Schweizer, 2000; Schweizer et al., 2006; Söderlund, Parker, Schwartz, & Tulving, 2005), and concluded that acute tolerance occurred after observing the absence of an effect of alcohol on the descending limb, which

had been present on the descending limb. Although the inclusion of this criterion in the present study prohibits concluding acute tolerance occurred in the low dose-condition, it increases confidence that the effect actually occurred in the high-dose condition. One potential reason for the absence of effect in the low-dose condition is type-2 error due to insufficient statistical power. However, this seems unlikely given both the size of the sample used, and the results of the Bayesian analysis which found a low likelihood of effect in the data produced.

Another potential reason for the absence of acute tolerance in the low dose condition is the difference in the absorption time of each dose. In the peak comparison paradigm, the high dose condition reached peak BAC 22 minutes later than in the low dose condition, allowing for a greater delay after peak subjective intoxication, which occurred at a similar time between groups. In the Mellanby paradigm, the difference in absorption (and elimination) time between doses resulted in ascending limb measures being taken 69 minutes later in the high dose condition, allowing more time for a noticeable decrease in dose-effect to develop. However, this is not consistent with the finding of the rate of recovery paradigm, which would have shown a faster rate of recovery for subjective intoxication in the low dose condition if acute tolerance had occurred.

The current findings from the peak comparison paradigm are consistent with the previous findings from Radlow and Hurst (1985) who found peak BAC occurred 24 minutes after peak drug-effect from a dose of 1g/kg; higher than the dose used in the present study. The similar times of peak subjective intoxication in both dose groups suggests that the higher dose did not prolong the length of time before reaching peak intoxication. Our finding of acute tolerance to subjective intoxication with the rate of recovery paradigm is also consistent with the finding of Martin and Moss (1993). The faster rate of recovery from the subjective intoxication (relative to BAC) in the high dose condition is an important finding, as it supports the theory that higher doses will produce a greater degree of acute tolerance. In a real-world context, the occurrence of peak intoxication substantially ahead of peak BAC and the faster relative rate of recovery could produce a diminishing returns scenario in cases of binge drinking. The high doses used to produce the magnitude of intoxication being sought would produce tolerance resulting in even larger doses being consumed, which may lead to dangerously high BACs.

There are other paradigms that have been used to examine acute tolerance which were not included in the current study, primarily due to their requiring different measurement and dosing protocols not shared by the three paradigms used. The steady-state paradigm examines acute

tolerance by observing changes in drug-effect while BAC is held constant (Kaplan, Sellers, Hamilton, Naranjo, & Dorian, 1985). In recent years the development of technology enabling an intravenous infusion of alcohol to be used to provide a constant dose to maintain a constant BAC has allowed for the steady-state paradigm to be more precise (Hiltunen, Saxon, Skagerberg, & Borg, 2000). Given the differential finding of acute tolerance between dose sizes observed in the current study, it is suggested that the steady-state paradigm be used in future studies to compare the effect between different sizes of dose. Although the use of intravenous doses has less ecological validity in comparison to oral administration, subjective responses have been found to be equivalent between routes of administration (Plawecki et al 2019). As is typical of psychological research, our sample was drawn entirely from an undergraduate student population, which somewhat limits its generalizability. Individual differences to subjective responses are implicated in the risk for alcohol use disorders and alcohol-related harms (King, De Wit, McNamara, & Cao, 2011). Therefore, it is recommended that samples of both more general, and more specific populations be used in future research.

In conclusion, this study examined acute tolerance to subjective intoxication using three different paradigms. All three paradigms were consistent in finding acute tolerance only in the high dose condition. While this suggests that acute tolerance only develops under higher doses, this finding should be interpreted with caution as the effect has been found in other studies under lower dose sizes. The consistency of the results in this study demonstrates the increased robustness afforded by the use of multiple paradigms. Given the simplicity and ease of using multiple paradigms when examining the effect in measures like subjective intoxication, we suggest the practice be adopted in future studies. However, for more time-consuming measures, particularly objective behavioural measures like cognitive tasks, the inclusion of multiple paradigms may be difficult if the paradigms require frequent measures.

References

Aston, E. R., & Liguori, A. (2013). Self-estimation of blood alcohol concentration: A review. *Addictive Behaviors, 38*(4), 1944-1951.

Banks, W. P., Vogler, R. E., & Weissbach, T. A. (1979). Adaptation of ethanol intoxication. *Bulletin of the Psychonomic Society, 14*(5), 319-322.

Comley, R. E., & Dry, M. J. (2020-a). Acute behavioral tolerance to alcohol. *Experimental and clinical psychopharmacology*, *28*(1), 112.

Comley, R. E., & Dry, M. J. (2020-b). Acute tolerance to alcohol-induced impairment in cognitive performance. *Experimental and Clinical Psychopharmacology*.

Earleywine, M., & Erblich, J. (1996). A confirmed factor structure for the Biphasic Alcohol Effects Scale. *Experimental and Clinical Psychopharmacology, 4*(1), 107-113.

Ellinwood, E. H., Jr., Linnoila, M., Easler, M. E., & Molter, D. W. (1981). Onset of peak impairment after diazepam and after alcohol. *Clin Pharmacol Ther, 30*(4), 534-538.

Fillmore, M. T., Dixon, M. J., & Schweizer, T. A. (2000). Alcohol affects processing of ignored stimuli in a negative priming paradigm. *Journal of Studies on Alcohol*, 61(4), 571-578.

Fillmore, M. T., Marczinski, C. A., & Bowman, A. M. (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *J Stud Alcohol*, 66(5), 663-672.

Gengo, F. M., Gabos, C., Straley, C., & Manning, C. (1990). The Pharmacodynamics of Ethanol: Effects on Performance and Judgment. *The Journal of Clinical Pharmacology, 30*(8), 748-754. doi: 10.1002/j.1552-4604.1990.tb03638.x

Hendershot, C. S., Wardell, J. D., Strang, N. M., Markovich, M. S., Claus, E. D., & Ramchandani, V. A. (2015). Application of an alcohol clamp paradigm to examine inhibitory control, subjective responses, and acute tolerance in late adolescence. *Exp Clin Psychopharmacol, 23*(3), 147-158. doi: 10.1037/pha0000017

Hiltunen, A. J., Saxon, L., Skagerberg, S., & Borg, S. (2000). Acute tolerance during intravenous infusion of alcohol: comparison of performance during ascending and steady state concentrations--a pilot study. *Alcohol, 22*(2), 69-74.

Kalant, H. (1996). Current state of knowledge about the mechanisms of alcohol tolerance. *Addiction Biology, 1*(2), 133-141. doi: 10.1080/1355621961000124756

Kaplan, H. L., Sellers, E. M., Hamilton, C., Naranjo, C. A., & Dorian, P. (1985). Is there acute tolerance to alcohol at steady state? *J Stud Alcohol, 46*(3), 253-256.

King, A. C., De Wit, H., McNamara, P. J., & Cao, D. (2011). Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Archives of General Psychiatry, 68*(4), 389-399.

Martin, C. S., & Moss, H. B. (1993). Measurement of acute tolerance to alcohol in human subjects. *Alcohol Clin Exp Res, 17*(2), 211-216.

Mellanby, E. (1919). *Alcohol: Its absorption into and disappearance from the blood under different conditions* (Special Report Series No. 31). London, England: Medical Research Committee.

Nicholson, M. E., Wang, M., Airhihenbuwa, C. O., Mahoney, B. S., Christina, R., & Maney, D. W. (1992). Variability in behavioral impairment involved in the rising and falling BAC curve. *Journal of Studies on Alcohol, 53*(4), 349-356.

Plawecki, M. H., Durrani, A. M., Boes, J., Wetherill, L., Kosobud, A., O'Connor, S., & Ramchandani, V. A. (2019). Comparison of Subjective Responses to Oral and Intravenous Alcohol Administration Under Similar Systemic Exposures. *Alcoholism: Clinical and Experimental Research*, 43(4), 597-606.

Post, R. B., Tavano, L. A., & Maddock, R. J. (1998). Role of feedback in formation of acute tolerance to alcohol. *Journal of Studies on Alcohol, 59*(6), 723.

Radlow, R. (1994). A quantitative theory of acute tolerance to alcohol. *Psychopharmacology (Berl), 114*(1), 1-8.

Radlow, R., & Hurst, P. M. (1985). Temporal relations between blood alcohol concentration and alcohol effect: an experiment with human subjects. *Psychopharmacology, 85*(3), 260-266. doi: 10.1007/BF00428184

Rigter, H., & Crabbe, J. C. (1980). *Alcohol tolerance and dependence*. Amsterdam New York : New York: Elsevier/North-Holland Biomedical Press sole distributors for the U.S.A. and Canada, Elsevier/North Holland.

Saunders, J. B., Aasland, O. G., Babor, T. F., De la Fuente, J. R., & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*, 88(6), 791-804.

Schweizer, T. A., Jolicœur, P., Vogel-Sprott, M., & Dixon, M. J. (2004). Fast, but Error-Prone, Responses During Acute Alcohol Intoxication: Effects of Stimulus-Response Mapping Complexity. *Alcoholism: Clinical and Experimental Research*, 28(4), 643-649.

Schweizer, T. A., Vogel-Sprott, M., Danckert, J., Roy, E. A., Skakum, A., & Broderick, C. E. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacology*, 31(6), 1301-1309.

Söderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology*, 182(2), 305-317. doi: 10.1007/s00213-005-0096-2

Starkey, N. J., & Charlton, S. G. (2014). The effects of moderate alcohol concentrations on driving and cognitive performance during ascending and descending blood alcohol concentrations. *Hum Psychopharmacol, 29*(4), 370-383. doi: 10.1002/hup.2415

Streufert, S., Pogash, R. M., Roache, J., Gingrich, D., Landis, R., Severs, W., . . . Kantner, A. (1992). Effects of alcohol intoxication on risk taking, strategy, and error rate in visuomotor performance. *Journal of Applied Psychology, 77*(4), 515-524.

Tupler, L., Hege, S., & Ellinwood, E. (1995). Alcohol pharmacodynamics in young-elderly adults contrasted with young and middle-aged subjects. *Psychopharmacology, 118*(4), 460-470.

Vogel-Sprott, M., & Fillmore, M. T. (1993). Impairment and recovery under repeated doses of alcohol: Effects of response-outcomes. *Pharmacology, Biochemistry and Behavior, 45*(1), 59-63. doi: 10.1016/0091-3057(93)90086-9

Watson, P. E., Watson, I. D., & Batt, R. D. (1981). Prediction of blood alcohol concentrations in human subjects. Updating the Widmark Equation. *Journal of Studies on Alcohol, 42*(7), 547-556.

Chapter 4: Conclusions

4.1 Summary of papers

This thesis aimed to address limitations in the current understanding of acute tolerance. Specifically, which cognitive domains it occurs in, what effect the size of the dose has, and whether findings are consistent across paradigms. The literature review provided an up-to-date summation of the literature on empirical studies of the effect. Our review included a larger sample of studies than previous reviews and the inclusion of several different paradigms provided a more comprehensive synopsis of the current literature. In addition, we were able to clarify the conflicting findings in the past reviews by Holland and Ferner (2017) and by Schweizer and Vogel-Sprott (2008). Our review also identified gaps in our knowledge about which objective measures show acute tolerance and what influence the size of the dose has on the effect. Our three experimental studies tested acute tolerance in subjective intoxication and across several cognitive domains, examined the effect of dose-size, and compared analyses of the same data between multiple paradigms. Acute tolerance was found in information processing speed using the Mellanby paradigm, and in subjective intoxication using the Mellanby, peak comparison, and rate of recovery paradigms.

Our findings of acute tolerance to subjective intoxication were not a novel or unexpected finding. The literature review clearly indicated that subjective measures would reliably show acute tolerance, and hence the VAS was used alongside objective measures as an indicator for whether any acute tolerance had developed. The VAS showed the effect in each experiment under peak BACs of 0.07% and 0.08% respectively. Although these findings are not novel, they do add further weight to the body of evidence that practically confirms that the effect occurs in subjective intoxication measures. In addition, we also used the subjective intoxication measure to conduct a unique comparison between three different paradigms for testing acute tolerance. This was the first paper to examine and compare the effect between the Mellanby, Rate of Recovery, and peak comparison paradigms using the same data. The consistency of the results between the paradigms was an important finding, showing the effect occurring beyond the conditions of the Mellanby paradigm.

Although the effect of dose size was unable to be analysed with the data from the objective measures in the second study (as no acute tolerance was found) this was not the case with the VAS. Acute tolerance to subjective intoxication was not found in the lower dose condition using any of the paradigms, but all three paradigms showed acute tolerance under the higher dose, which is consistent with the theory that the effect is more likely at high doses.

The most notable finding in this thesis was the acute tolerance to the impairment from alcohol on the ITT. We tested the measure under similar conditions to Cash et al. (2015) who did not find the effect. As discussed, their study used a cumulative dosing protocol, where part of the dose was administered after measures had been taken on the ascending limb. Whereas when we administered all measures after a single bolus dose, less impairment in ITT performance was found on the descending limb. The contrast between the findings of Cash et al. (2015) and Comley and Dry (2020-a) suggests that a research design using a bolus dose is more likely to find acute tolerance. This is consistent with both the pattern of results found in the literature review and the theory that acute tolerance is more likely with faster consumption. Cumulative doses are more similar to real-world consumption patterns and can produce a slower increase in the BAC than bolus doses. In research settings, either dosing protocol could be appropriate depending on the specific aims of the study.

Even though observing acute tolerance in ITT performance was an important finding, most of the cognitive measures tested did not show an acute tolerance effect. In most cases, this was simply because there was not sufficient impairment on the ascending limb to show recovery from. Although a sufficiently sized dose of alcohol will very reliably induce intoxication, measures of cognitive performance are less reliable in reflecting that state. For three of the measures used in the second study, we did not conclude that acute tolerance had developed despite showing both an effect of alcohol and a decrease in the effect between limbs. Reactive inhibition for the 20% condition in the SST in the low dose condition, accuracy on the MCRT in the high dose condition, and subjective intoxication in the low dose group, all had a smaller drug-effect on the descending limb than the ascending limb, but the decrease was not significantly different from the change seen in the placebo

group over the same period. The measures meeting some of the criteria does offer some justification for re-examination with greater statistical power.

Prior investigations of acute tolerance have not always explicitly stipulated their conditions for showing acute tolerance, or rationale for testing it, and as a result, different researchers have concluded the effect has or has not occurred using varying standards of evidence. In our studies we explicitly stated three criteria and our rationale for testing acute tolerance: i) an effect of alcohol on the ascending limb, ii) a smaller effect on the descending limb, iii) a statistically significant dose × limb interaction. The criterion of a statistically significant interaction between a placebo group and an active dose group, with the BAC limb confirms the observed decrease (criterion ii) is distinct from any decrease observed in the equivalent placebo conditions. The absence of acute tolerance on most of the objective measures we used was not entirely unexpected given the variability we found in the review, but it cannot be concluded that the effect does not occur in the domains of behaviour they measure from these findings alone. Repeating examination with the same measures should be encouraged to properly understand the pattern of effect in objective measures, and draw more definitive conclusions from a larger body of evidence.

4.2 Implications

The different pattern of acute tolerance between objective and subjective measures identified in our review was a concerning finding. This trend was also evident in the findings from the first study. We stated in Comley & Dry (2020-b) that "The magnitude of the acute tolerance observed in ITT performance and ratings of subjective intoxication cannot be equated between measures with such obvious conceptual differences." But still concluded that "…although cognitive performance in domains such as information processing speed may show statistically significant recovery from alcohol, it is unlikely to be clinically or ecologically significant to the degree that driving with an elevated BAC becomes safe." This conclusion was drawn largely on the absence of acute tolerance in simulated driving studies and the overall trend for objective measures (like those associated with driving) to show acute tolerance less often or reliably than subjective measures. This conclusion was also consistent with the findings of the second study, which showed a significant acute tolerance

effect for subjective intoxication, while the decrease in effect for objective measures was not large enough to show a statistically significant interaction.

This differential acute tolerance effect between subjective and objective measures is especially salient when we consider how it may translate into a real-world context. Laverty (1989) claimed that findings of acute tolerance could imply that alcohol-induced impairment of driving may be reduced if the driver were to wait until after the peak of the BAC curve[17]. However, none of the studies that have examined acute tolerance in driving ability thus far have found the effect in simulated driving measures. When we consider the autopsy data from Lahti et al., (2014) and Levine & Smialek (2000) that shows higher deaths in road accidents when BAC is decreasing, it becomes apparent that the reliable acute tolerance to subjective intoxication creates a unique risk when coupled with a different degree of recovery from objective impairment.

If the subjective effects of alcohol show more acute tolerance than objective effects, then intoxicated persons are likely to underestimate their level of intoxication and impairment. It has been repeatedly stated throughout this thesis that the reliable decrease in the subjective effects of alcohol has the potential to promote excess consumption. If drinkers are attempting to reach a particular level of intoxication, a decrease in the subjective effects will require larger doses to be consumed to produce the same degree of felt intoxication. Given the difference in acute tolerance between subjective and objective effects, this is also likely to lead to underestimations of impairment and increased potential of engaging in risky or unsafe behaviour. Consistent with this idea, studies comparing BACs from people in real-world drinking settings with their own ratings of intoxication consistently show that people with higher BACs tend to underestimate their BAC (Aston & Liguori, 2013). Also, studies comparing self-ratings of impairment with actual performance reliably find that people underestimate their impairment more as they become more intoxicated. We mentioned in Comley & Dry (2020-b) that "The degree of impairment that alcohol causes is often estimated based on the size of the dose alone, but estimates of the effects of alcohol could be made more accurate if changes in the dose effect were accounted for". The findings of this thesis clearly indicate that

[17] He does qualify this statement by noting that policy and research has not suggested this is the case.

subjective feelings of intoxication are an unreliable gauge of one's impairment. Which is of concern as they are also the most available cues in a real-world context.

Something else mentioned recurrently in this thesis has been the lack of attention health campaigns have paid to acute tolerance and similar effects. The WHO advises that people avoid drinking alcohol altogether, or at least minimize consumption. Organizations like the WHO prescribe drinking guidelines based on research correlating consumption with harms, from which it is logically inferred that reducing consumption will reduce the amount of harm. Although these prescribed patterns of consumption inform consumers about unhealthy levels of consumption and what the harms associated with greater levels are, they ignore people's reasons or aims for drinking (Lovatt, 2015; Müller & Schumann, 2011). Individuals have their own reasons for consumption, which should be considered in prescribing guidelines, in order to make them more applicable for a broader range of consumers. Understanding effects like acute tolerance could be incorporated into responsible drinking guidelines to help people achieve the aims of their drinking in the safest possible way, and be aware of the risk of harm such effects pose in terms of increased consumption and underestimation of intoxication. We found in the literature review that acute tolerance was more likely with rapid consumption, and in the second study that acute tolerance only occurred in the higher dose. This suggests that a decrease in the dose-effect of alcohol is more likely when drinking larger amounts more quickly. In applying these findings to guidelines someone wanting to minimize total consumption while reaching and maintaining a desired level of intoxication should aim to do so by using a slower consumption pattern in order to minimize acute tolerance.

4.3 Limitations

There are several limitations concerning the individual studies beyond those discussed in the manuscripts that I will address here. Firstly, a meta-analysis of acute tolerance findings was not conducted in the literature review because of the variability between studies (paradigm used, measures, dose, BACs measures were taken at, etc.) made comparisons of the effect sizes between the different studies meaningless. Secondly, the finding of acute tolerance in ITT performance adds further complexity to understanding what measures show the effect because it conflicts with the

findings of Cash et al. (2015). The primary modification to Cash et al. (2015) design was the difference in the consumption pattern, which offers a potential explanation for the two different findings, and was consistent with the pattern identified in the literature review. However, as this is only a single finding of the effect with the ITT, it requires that its reliability be addressed.

Not using the ITT as a task for the second study is a potential limitation of this research. The ITT was evidently more likely to show acute tolerance than the objective measures used in the second study and, therefore, may have been a better measure for examining the effect of dose-size. Subsequent testing with the ITT was not considered because the intention when initially planning the studies was to test for acute tolerance with a range of different behavioural measures. As the ITT showed acute tolerance in the first experiment under a peak BAC of .07%, comparing the effect under the doses in the second experiment of .06% and .08% would have allowed comparisons across three dose-sizes. Additionally, the ITT often does not require longer than one or two minutes to complete and is seen to be resistant to practice effects from multiple administrations (Preiss & Burns, 2012), which means that it could potentially have been a valid measure to compare under the different paradigms used in the third study.

Finally, an inherent limitation in the general field of alcohol research is the variability in BAC measurement. BAC produced from an orally administered dose can vary between individuals due to metabolic factors, gastrointestinal factors, body composition, genetics, chronic tolerance, etc. Measurement of BAC in our studies was taken via breathalyzer readings which are also subject to sources of error due to things like hiccupping and burping. Although these differences can be accounted for in the analysis and overcome through adequate statistical power, there are also administration and procedural methods that can be used to reduce it. The clamping procedure discussed in the literature review is such a method. We did not use an intravenous clamp in the studies for this thesis due to the cost, personnel and technical know-how required for the procedure, but given the advantages it has for accurately producing and maintaining a BAC, I predict studies using it to examine acute tolerance will become more popular.

4.4 Future Research

The considerations for future research discussed in each paper were largely focused on overcoming the limitations of each particular study. In the third study, we attempted to overcome some of the limitations of the Mellanby paradigm by analysing the data with multiple paradigms. This would often be difficult with measures that take a long time to administer or that should be limited in the number of administrations, but future research on acute tolerance would benefit from the greater rigour that comes from multiple analyses. In addition, researchers would benefit from using an intravenous clamp as the method of administration. Large samples tested under numerous paradigms with clamping to accurately produce or maintain a BAC will yield the most informative data on acute tolerance in the near future but only if it is undertaken.

In the literature review three major areas of focus for research on acute tolerance were discussed: increasing consistency in research designs, examining the effect with novel measures, and combined psychopharmacology research. The need for greater consistency in research designs to allow comparisons between studies is still present. One facet of study design consistency that we aimed to address in our studies was the criteria used to test for the Mellanby paradigm. Although many past studies have used uniform methods of analysis with Mellanby's design, the lack of an explicit list of criteria with a rationale for testing the effect has allowed for an inconvenient degree of variability between studies that makes comparisons more difficult.

If the volume of literature on acute tolerance continues to grow over the coming years and researchers do use comparable methods and measures, it may be possible to eventually conduct a meta-analysis on the topic. We attempted in our studies to examine the effect with novel measures to explore what domains show the effect, but in doing so we neglected to attempt to replicate the effect with the ITT in the second study. This highlights a trade-off between the value of testing for the effect with novel measures to determine if a particular behaviour shows the effect and testing with measures that have already shown the effect to ascertain how reliable it is.

In Comley and Dry (2020-a) and Comley and Dry (2020-b), combined psychopharmacology is mentioned as a viable avenue for research based on its real-world prevalence. I would still contend that there is value in knowing how acute tolerance changes when multiple substances are present. But due to the lack of reliable objective measures, studies would need to include a subjective measure to be confident of seeing an effect. Research on the effect in objective measures would benefit from a simpler study with just alcohol until which objective measures reliably show the effect is determined.

4.5 Summary

To conclude: Alcohol consumption has been a part of human behaviour since the beginning of our species, and it remains our species most popular and harmful drug. Understanding how alcohol affects behaviour is a valuable area of research for its potential to mitigate the harms that it causes. Acute tolerance is just one of an array of effects that contribute to the overall complexity of alcohol intoxication, but has obvious implications for real-world drinking behaviours and the associated harms. We reviewed the literature on acute tolerance, found the effect in information processing speed using the Mellanby paradigm, and in subjective intoxication with the Mellanby, peak comparison, and rate of recovery paradigms. The comparable findings between the different paradigms used add novel support to an already solid body of literature on the effect in subjective intoxication. The finding of acute tolerance in inspection time performance adds to a complex pattern of effect for objective measures that needs further research. Acute tolerance remains an area of research that deserves attention for the potential benefit it could have for reducing the harms caused by alcohol.

References

Agarwal, D. P., & Goedde, H. W. (2012). *Alcohol metabolism, alcohol intolerance, and alcoholism: Biochemical and pharmacogenetic approaches*: Springer Science & Business Media.

Ames, G. M., & Bennett, L. A. (2013). *The American experience with alcohol: Contrasting cultural perspectives*: Springer Science & Business Media.

Aston, E. R., & Liguori, A. (2013). Self-estimation of blood alcohol concentration: A review. *Addictive behaviors*, *38*(4), 1944-1951.

Banks, W. P., Vogler, R. E., & Weissbach, T. A. (1979). Adaptation of ethanol intoxication. *Bulletin of the Psychonomic Society, 14*(5), 319-322.

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). Neuroscience: Exploring the brain.

Beauvais, F. (1998). American Indians and alcohol. *Alcohol Research, 22*(4), 253.

Bennett, J. M. (1996). *Ale, beer, and brewsters in England: women's work in a changing world, 1300-1600*: Oxford University Press.

Bennett, R. H., Cherek, D. R., & Spiga, R. (1993). Acute and chronic alcohol tolerance in humans: effects of dose and consecutive days of exposure. *Alcohol Clin Exp Res, 17*(4), 740-745.

Bloomfield, K., Stockwell, T., Gmel, G., & Rehn, N. (2003). International comparisons of alcohol consumption. *Alcohol Research & Health, 27*(1), 95.

Bonomo, Y., Norman, A., Biondo, S., Bruno, R., Daglish, M., Dawe, S., . . . Lenton, S. (2019). The Australian drug harms ranking study. *Journal of Psychopharmacology, 33*(7), 759-768.

Brussen, K. A. (2010). The Australian Guidelines to Reduce Health Risks from Drinking Alcohol. *Chisholm Health Ethics Bulletin, 15*(3), 9.

Bryceson, D. F. (2002). Alcohol in Africa: mixing business, pleasure, and politics.

Bushman, B. J. (1997). Effects of alcohol on human aggression: validity of proposed explanations.

Carrigan, M. (2019). Hominoid Adaptation to Dietary Ethanol. *Alcohol and Humans: A Long and Social Affair*, 24.

Cash, C., Peacock, A., Barrington, H., Sinnett, N., & Bruno, R. (2015). Detecting impairment: Sensitive cognitive measures of dose-related acute alcohol intoxication. *Journal of Psychopharmacology, 29*(4), 436-446.

Comley, R. E., & Dry, M. J. (2020-a). Acute behavioral tolerance to alcohol. *Experimental and Clinical Psychopharmacology, 28*(1), 112.

Comley, R. E., & Dry, M. J. (2020-b). Acute tolerance to alcohol-induced impairment in cognitive performance. *Experimental and Clinical Psychopharmacology*.

Comley, R. E., & Dry, M. J. (Under Review-a). Acute tolerance to alcohol in objective and subjective measures.

Comley, R. E., & Dry, M. J. (Under Review-b). Acute tolerance to subjective intoxication from alcohol.

Connor, J. P., Haber, P. S., & Hall, W. D. (2016). Alcohol use disorders. *The Lancet, 387*(10022), 988-998.

Cook, C., Creyke, R., Geddes, R., & Hamer, D. (2009). *Laying down the law*. LexisNexis Butterworths.

COTSEN, L. Celebrating Life in Mesopotamia.

Crow, K. E., & Batt, R. D. (1989). *Human metabolism of alcohol*. Boca Raton, Fla: CRC Press.

da Silva Lopes, T. (2002). Brands and the evolution of multinationals in alcoholic beverages. *Business History*, *44*(3), 1-30.

Danielsson, O., & Jörnvall, H. (1992). " Enzymogenesis": classical liver alcohol dehydrogenase origin from the glutathione-dependent formaldehyde dehydrogenase line. *Proceedings of the National Academy of Sciences, 89*(19), 9247-9251.

Dasgupta, A. (2011). *The science of drinking : how alcohol affects your body and mind*. Lanham [Md: Rowman & Littlefield Pub.

Dashko, S., Zhou, N., Compagno, C., & Piškur, J. (2014). Why, when, and how did yeast evolve alcoholic fermentation? *FEMS yeast research, 14*(6), 826-832.

Deitrich, R. A., & Erwin, V. G. (1995). *Pharmacological effects of ethanol on the nervous system* (Vol. 32): CRC Press.

Dietler, M. (2006). Alcohol: Anthropological/archaeological perspectives. *Annu. Rev. Anthropol., 35*, 229-249.

DrinkwiseAustralia. (2019). Tips to help you drink properly. Retrieved from https://drinkwise.org.au/drinking-and-you/tips-to-help-you-drink-properly/#

Dry, M. J., Burns, N. R., Nettelbeck, T., Farquharson, A. L., & White, J. M. (2012). Dose-related effects of alcohol on cognitive functioning. *PloS one, 7*(11), e50977.

Dudley, R. (2000). Evolutionary origins of human alcoholism in primate frugivory. *The Quarterly Review of Biology, 75*(1), 3-15.

Dudley, R. (2004). Ethanol, Fruit Ripening, and the Historical Origins of Human Alcoholism in Primate Frugivory1. *Integrative and Comparative Biology, 44*(4), 315-323. doi: 10.1093/icb/44.4.315

Dunbabin, K. M. (1993). Wine and water at the Roman convivium. *Journal of Roman Archaeology, 6*, 116-141.

Edward, K.-L. (2013). *Psychopharmacology : practice and contexts*. South Melbourne, Victoria: Oxford University Press.

Ellinwood, E. H., Jr., Linnoila, M., Easler, M. E., & Molter, D. W. (1981). Onset of peak impairment after diazepam and after alcohol. *Clin Pharmacol Ther, 30*(4), 534-538.

Ferner, R. E., Holland, M. G., Sullivan, R. W., & Dufol, A. F. (2016). The evidence for acute tolerance to human alcohol intoxication (the Mellanby effect): A systematic review. *Clinical Toxicology, 54*(4), 484-485.

Fillmore, M. T., & Vogel- Sprott, M. (1998). Behavioral impairment under alcohol: cognitive and pharmacokinetic factors. *Alcoholism: Clinical and Experimental Research, 22*(7), 1476-1482.

Fogarty, J. N., & Vogel-Sprott, M. (2002). Cognitive processes and motor skills differ in sensitivity to alcohol impairment. *Journal of Studies on Alcohol, 63*(4), 404-411.

Fox, A., & MacAvoy, M. (2010). Four hundred rabbits: expressions of drunkenness. *Four hundred rabbits: expressions of drunkenness.*

Gately, I. (2008). *Drink: A cultural history of alcohol*: Penguin.

Gift, A. G. (1989). Visual analogue scales: measurement of subjective phenomena. *Nursing research, 38*(5), 286-287.

Ginsburg, B. C., Martinez, G., Friesenhahn, G., Javors, M., & Lamb, R. J. (2008). Acute tolerance to rate-decreasing effects of single doses of ethanol. *Physiol Behav, 94*(3), 374-383. doi: 10.1016/j.physbeh.2008.01.026

Graham, K. M. (2008). *Raising the bar : preventing aggression in and around bars, pubs and clubs*. Cullompton, UK: Willan.

Gutzke, D. W. (2006). *Pubs and Progressives: reinventing the public house in England, 1896-1960*: Northern Illinois University Press.

Hagman, A., Säll, T., Compagno, C., & Piskur, J. (2013). Yeast "make-accumulate-consume" life strategy evolved as a multi-step process that predates the whole genome duplication. *PloS one, 8*(7), e68734.

Hames, G. (2014). *Alcohol in world history*: Routledge.

Hanson, D. (2013). Historical evolution of alcohol consumption in society. *Alcohol: Science, policy and public health*, 4-14.

Hart, C. L., Ksir, C., & Ray, O. S. (2013). *Drugs, society & human behavior*: McGraw-Hill New York, NY.

Hayashida, F. M. (2008). Ancient beer and modern brewers: Ethnoarchaeological observations of chicha production in two regions of the North Coast of Peru. *Journal of Anthropological Archaeology, 27*(2), 161-174.

Healey, J. (2011). *Alcohol and binge drinking*. Thirroul, N.S.W: Spinney Press.

Hendershot, C. S., Wardell, J. D., Strang, N. M., Markovich, M. S., Claus, E. D., & Ramchandani, V. A. (2015). Application of an alcohol clamp paradigm to examine inhibitory control, subjective responses, and acute tolerance in late adolescence. *Exp Clin Psychopharmacol, 23*(3), 147-158. doi: 10.1037/pha0000017

Hingson, R. W., & White, A. (2013). Trends in extreme binge drinking among US high school seniors. *JAMA Pediatrics, 167*(11), 996-998.

Hoffman, P. L., & Tabakoff, B. (1996). Alcohol dependence: a commentary on mechanisms. *Alcohol and Alcoholism, 31*(4), 333-340.

Holland, M. G., & Ferner, R. E. (2017). A systematic review of the evidence for acute tolerance to alcohol–the "Mellanby effect". *Clinical Toxicology, 55*(6), 545-556.

ISWR. (2019). Worldwide Alcohol Consumption Declines -1.6%. Retrieved 2020, from https://www.theiwsr.com/news-and-comment-worldwide-alcohol-consumption-declines/

Jellinek, E. M., & McFarland, R. A. (1940). Analysis of psychological experiments on the effects of alcohol. *Quarterly journal of studies on alcohol*.

Jennings, J., Antrobus, K., Atencio, S., Glavich, E., Johnson, R., Loffler, G., . . . Hayden, B. (2005). "Drinking Beer in a Blissful Mood" Alcohol Production, Operational Chains, and Feasting in the Ancient World. *Current Anthropology, 46*(2), 275-303.

Johnson, H. (1989). *Vintage: The story of wine*: Simon and Schuster.

Jones, B. M., & Vega, A. (1972). Cognitive performance measured on the ascending and descending limb of the blood alcohol curve. *Psychopharmacologia, 23*(2), 99-114.

Julien, R. M. (2008). *A primer of drug action : a comprehensive guide to the actions, uses, and side effects of psychoactive drugs* (11th ed. / Robert M. Julien, Claire D. Advokat, Joseph E. Comaty. ed.). New York, NY: Worth Publishers.

Kahler, C. W., McCrady, B. S., & Epstein, E. E. (2003). Sources of distress among women in treatment with their alcoholic partners. *Journal of Substance Abuse Treatment, 24*(3), 257-265.

Kaplan, H. L., Sellers, E. M., Hamilton, C., Naranjo, C. A., & Dorian, P. (1985). Is there acute tolerance to alcohol at steady state? *J Stud Alcohol, 46*(3), 253-256.

Katz, S. H., & Voigt, M. M. (1986). Bread and beer. *Expedition, 28*(2), 23-34.

Kosobud, A. E., Wetherill, L., Plawecki, M. H., Kareken, D. A., Liang, T., Nurnberger, J. L., . . . O'Connor, S. J. (2015). Adaptation of Subjective Responses to Alcohol is Affected by an Interaction of GABRA2 Genotype and Recent Drinking. *Alcohol Clin Exp Res, 39*(7), 1148-1157. doi: 10.1111/acer.12749

Kuhn, C. (1998). *Buzzed : the straight facts about the most used and abused drugs from alcohol to ecstasy*. New York: W.W. Norton.

Kurtzman, C. P., & Fell, J. W. (2006). Yeast systematics and phylogeny—implications of molecular identification methods for studies in ecology. In *Biodiversity and ecophysiology of yeasts* (pp. 11-30): Springer.

Lahti, R. A., Pitkäniemi, J., Jones, A. W., Sajantila, A., Poikolainen, K., & Vuori, E. (2014). Cause and manner of death and phase of the blood alcohol curve. *Forensic Science International, 244*, 306-312. doi: 10.1016/j.forsciint.2014.09.015

Laverty, R. (1989). Tolerance to alcohol and its relationship to dependence. In K. E. Crow & R. D. Batt (Eds.), *Human metabolism of alcohol* (Vol. 3). Boca Raton, Fla: CRC Press.

Le, A. D., & Mayer, J. M. (1996). Aspects of alcohol tolerance in humans and experimental animals. *Pharmacological effects of ethanol on the nervous system*, 251-268.

Leonard, B. E. (2003). *Fundamentals of psychopharmacology* (3rd ed. ed.). Chichester ;: J. Wiley.

Levine, B., & Smialek, J. E. (2000). Status of alcohol absorption in drinking drivers killed in traffic accidents. *Journal of Forensic Sciences, 45,* 3–6. http://dx.doi.org/10.1520/JFS14632J

Liu, L., Wang, J., Rosenberg, D., Zhao, H., Lengyel, G., & Nadel, D. (2018). Fermented beverage and food storage in 13,000 y-old stone mortars at Raqefet Cave, Israel: Investigating Natufian ritual feasting. *Journal of Archaeological Science: Reports, 21*, 783-793.

Lovatt, M. (2015). Alcohol guidelines ignore how people drink – that's why they're not heeded. Retrieved 2020, from https://theconversation.com/alcohol-guidelines-ignore-how-people-drink-thats-why-theyre-not-heeded-45675

Mager, A. (2005). 'One Beer, One Goal, One Nation, One Soul': South African Breweries, Heritage, Masculinity and Nationalism 1960–1999. *Past & present, 188*(1), 163-194.

Martin, A. (2001). Lynn: Alcohol, Sex, and Gender in Late Medieval and Early Modern Europe. *Basingstoke, Hampshire et al*.

Martin, C. S., & Moss, H. B. (1993). Measurement of acute tolerance to alcohol in human subjects. *Alcohol Clin Exp Res, 17*(2), 211-216.

Martin, S. C. (2014). *The sage encyclopedia of alcohol: Social, cultural, and historical perspectives*: SAGE Publications.

McGovern, P. E. (2009). *Uncorking the past: the quest for wine, beer, and other alcoholic beverages*: Univ of California Press.

McKenna, T. (1999). *Food of the Gods: The Search for the Original Tree of Knowledge: A radical history of plants, drugs and human evolution*: Random House.

McNaught, A. D., & McNaught, A. D. (1997). *Compendium of chemical terminology* (Vol. 1669): Blackwell Science Oxford.

Mellanby, S. E. (1919). *Alcohol: its absorption into and disappearance from the blood under different conditions*: The University Press.

Meyer, J. S., & Quenzer, L. F. (2005). *Psychopharmacology: Drugs, the brain, and behavior*: Sinauer Associates.

Miller, M. A., & Fillmore, M. T. (2014). Protracted impairment of impulse control under an acute dose of alcohol: A time-course analysis. *Addictive Behaviors, 39*(11), 1589-1596. doi: 10.1016/j.addbeh.2013.10.035

Mitis, F., & Sethi, D. (2012). Reducing injuries and death from alcohol-related road crashes.

Møller, L. (2019). Q&A – How can I drink alcohol safely? Retrieved 2020, from https://www.euro.who.int/en/health-topics/disease-prevention/alcohol-use/data-and-statistics/q-and-a-how-can-i-drink-alcohol-safely

Mozayani, A., & Raymon, L. (Eds.). (2003). Handbook of drug interactions: a clinical and forensic guide. Springer Science & Business Media

Müller, C. P., & Schumann, G. (2011). Drugs as instruments: A new framework for non-addictive psychoactive drug use. *Behavioral and Brain Sciences, 34*(6), 293-310.

National Center for Biotechnology Information (2020). PubChem Compound Summary for CID 702, Ethanol. Retrieved September 9, 2020 from https://pubchem.ncbi.nlm.nih.gov/compound/Ethanol.

Nelson, M. (2005). *The barbarian's beverage: a history of beer in ancient Europe*: Routledge.

Ostling, E. W., & Fillmore, M. T. (2010). Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior. *Psychopharmacology (Berl), 212*(4), 465-473. doi: 10.1007/s00213-010-1972-y

Patrick, M. E. (2016). A call for research on high-intensity alcohol use. *Alcoholism, clinical and experimental research, 40*(2), 256.

Phillips, R. (2014). *Alcohol: a history*: UNC Press Books.

Pietrzykowski, A. Z., & Treistman, S. N. (2008). The molecular basis of tolerance. *Alcohol Res Health, 31*(4), 298-309.

Pohorecky, L. A., & Brick, J. (1990). Pharmacology of ethanol. *Balfour, D J K [Ed] (1990) Psychotropic drugs of abuse (pp 189-281) xiv, 497 pp Elmsford, NY, US: Pergamon Press; US*, 189-281.

Preiss, A. K., & Burns, N. R. (2012). Accurately measuring inspection time with computers.

Pryor, A. (2015). The industrialisation of the London Brewing Trade: Part I. *Brewery History, 161*, 51-90.

Radlow, R. (1994). A quantitative theory of acute tolerance to alcohol. *Psychopharmacology (Berl), 114*(1), 1-8.

Radlow, R., & Hurst, P. M. (1985). Temporal relations between blood alcohol concentration and alcohol effect: an experiment with human subjects. [Article]. *Psychopharmacology, 85*(3), 260-266. doi: 10.1007/BF00428184

Rigter, H., & Crabbe, J. C. (1980). *Alcohol tolerance and dependence*. Amsterdam New York : New York: Elsevier/North-Holland Biomedical Press sole distributors for the U.S.A. and Canada, Elsevier/North Holland.

Ritchie, H., & Roser, M. (2019). Alcohol Consumption. Retrieved 2020, from https://ourworldindata.org/alcohol-consumption

Roberts, C., & Robinson, S. (2007). Alcohol concentration and carbonation of drinks: the effect on blood alcohol levels. *Journal of Forensic and Legal Medicine, 14*(7), 398-405.

Robinson, J., & Harding, J. (2015). *The Oxford companion to wine*: American Chemical Society.

Rudgley, R. (1994). *Essential substances: a cultural history of intoxicants in society*: Kodansha International.

Savoie, T. M., Emory, E. K., & Moody-Thomas, S. (1988). Acute alcohol intoxication in socially drinking female and male offspring of alcoholic fathers. *J Stud Alcohol, 49*(5), 430-435.

Scholliers, P. (2001). *Food, drink and identity: cooking, eating and drinking in Europe since the Middle Ages*: Berg Oxford.

Schweizer, T. A., & Vogel-Sprott, M. (2008). Alcohol-impaired speed and accuracy of cognitive functions: a review of acute tolerance and recovery of cognitive performance. *Exp Clin Psychopharmacol, 16*(3), 240-250. doi: 10.1037/1064-1297.16.3.240

Singh, N. L., Mishra, P., Shukla, S., Kumar, J., & Singh, R. (2010). 02. ALCOHOLIC FERMENTATION TECHNIQUES IN EARLY INDIAN TRADITION.

Smith, F. H. (2004). Spirits and Spirituality: Enslaved Persons and Alcohol in West Africa and the British and French Caribbean1. *The Journal of Caribbean History, 38*(2), 279.

Smith, F. H. (2008). *The archaeology of alcohol and drinking*. Gainesville: University Press of Florida.

South, D., & Hawthorn, V. (1990). Changing drinking and driving patterns: a case history. *Alcohol and Crime. Canberra: Australian Institute of Criminology*, 107-119.

Statista. (u,d). Alcoholic Drinks. Retrieved 2020, from https://www.statista.com/outlook/10000000/100/alcoholic-drinks/worldwide

Steele, C. M., & Josephs, R. A. (1990). Alcohol myopia: Its prized and dangerous effects. *American psychologist, 45*(8), 921.

Stewart, J., & Badiani, A. (1993). Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol, 4*(4), 289-312.

Tabakoff, B., Melchior, C. L., & Hoffman, P. L. (1982). Commentary on Ethanol Tolerance. *Alcoholism: Clinical and Experimental Research, 6*(2), 252-259. doi: 10.1111/j.1530-0277.1982.tb04971.x

Taylor, B. J., Shield, K. D., & Rehm, J. T. (2011). Combining best evidence: a novel method to calculate the alcohol-attributable fraction and its variance for injury mortality. *BMC Public Health, 11*(1), 265.

UN. (1997). Glossary of environment statistics, studies in methods. *United Nations New York, NY*.

Unger, R. W. (2004). *Beer in the Middle Ages and the Renaissance*: University of Pennsylvania Press.

Vaccarino, F. (2004). *Neuroscience of psychoactive substance use and dependence*: World Health Organization.

van Wolputte, S., & Fumanti, M. (2010). *Beer in Africa: drinking spaces, states and selves* (Vol. 36): LIT Verlag Münster.

VandenBos, G. R. (2007). *APA dictionary of psychology*: American Psychological Association.

Vogel-Sprott, M. (1979). Acute recovery and tolerance to low doses of alcohol: differences in cognitive and motor skill performance. *Psychopharmacology, 61*(3), 287-291.

Wagner, J. (1972). Variations in absorption and elimination rates of ethyl alcohol in a single subject.

Watson, P. E., Watson, I. D., & Batt, R. D. (1981). Prediction of blood alcohol concentrations in human subjects. Updating the Widmark Equation. *Journal of Studies on Alcohol, 42*(7), 547-556.

WHO. (1992). International statistical classification of diseases and related health problems: 10th revision (ICD-10). *World health Organization*.

WHO. (2014). *Global status report on alcohol and health 2014* (2014 ed. ed.). Geneva: World Health Organization.

WHO. (2019). *Global status report on alcohol and health 2018*: World Health Organization.

Wiens, F., Zitzmann, A., Lachance, M.-A., Yegles, M., Pragst, F., Wurst, F. M., . . . Spanagel, R. (2008). Chronic intake of fermented floral nectar by wild treeshrews. *Proceedings of the National Academy of Sciences, 105*(30), 10426-10431.

Wilson, J. R., Erwin, V. G., & McClearn, G. E. (1984). Effects of ethanol: I. Acute metabolic tolerance and ethnic differences. *Alcoholism: Clinical and Experimental Research, 8*(2), 226-232.

Wilson, J. R., & Nagoshi, C. T. (1987). One-month repeatability of alcohol metabolism, sensitivity and acute tolerance. *J Stud Alcohol, 48*(5), 437-442.

Winstock, A. R., Barratt, M., Maier, L. J., & Ferris, J. A. (2018). Global drug survey 2018-key findings report. *Global Drug Survey*.

Zielinski, S. (2011). The Alcoholics of the Animal World. Retrieved 2020, from https://www.smithsonianmag.com/science-nature/the-alcoholics-of-the-animal-world-81007700/

Zoethout, R. W., Schoemaker, R. C., Zuurman, L., van Pelt, H., Dahan, A., Cohen, A. F., & van Gerven, J. M. (2009). Central nervous system effects of alcohol at a pseudo-steady-state concentration using alcohol clamping in healthy volunteers. *Br J Clin Pharmacol, 68*(4), 524-534. doi: 10.1111/j.1365-2125.2009.03488.x