ABSTRACT

The Effect of Alcohol Cue Exposure on Working Memory in Individuals with Alcohol Use Disorder

Katherine R. L'Esperance, Psy.D.

Mentor: Sara L. Dolan, Ph.D.

Alcohol use disorder (AUD) represents a grave public health concern in the U.S. with high prevalence and relapse rates, and a major risk factor for relapse is inability to cope with cravings. A possible explanatory factor is the experience of working memory impairment in individuals with AUD. The present study sought to demonstrate the effect of imaginal alcohol cue exposure on distress level, alcohol craving, and working memory performance to establish a possible pathway by which coping skill use is impaired in individuals with AUD during cravings. The study utilized a repeated-measures design to test working memory performance and examine subjective report of cue reactivity and objective arousal (i.e., blood pressure and heart rate) before and after a cue exposure. The sample consisted of 91 participants with AUD in residential substance use treatment, with 46 participants randomly assigned to the neutral-cue group and 45 participants to the alcohol-cue group. A repeated-measures ANOVA revealed a statistically significant effect of time and condition on subjective distress, $F(1,89) = 4.72$, $p = .032$, partial $\eta^2 = .05$, and alcohol craving as measured by a single-item rating, $F(1,89) = 5.79$, $p = .018$,

partial $\eta^2 = .06$; however, working memory performance improved from pre- to post-cue exposure for both groups. While results showed a statistically significant interaction between time and condition for heart rate, $F(2.46,162.32) = 5.77$, $p = .002$, partial $\eta^2 = .08$, heart rate remained stable from baseline to cue exposure in the alcohol cue group. Additionally, there was no significant difference in systolic or diastolic blood pressure between groups. Results suggest that individuals with AUD subjectively experience craving during an alcohol cue reactivity paradigm, but that working memory performance is unaffected by exposure to alcohol cues. Further, results are indicative of an attenuated cardiovascular response to stress and alcohol cue exposure.

The Effect of Alcohol Cue Exposure on Working Memory in Individuals with Alcohol Use Disorder

by

Katherine R. L'Esperance, B.A., M.S.C.P.

A Dissertation

Approved by the Department of Psychology and Neuroscience

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Charles A. Weaver III, Ph.D., Chairperson

Submitted to the Graduate Faculty of
Baylor University in Partial Fulfillment of the
Requirements for the Degree
of

Doctor of Psychology

Approved by the Dissertation Committee

_____

Sara L. Dolan, Ph.D., Chairperson

_____

Jim H. Patton, Ph.D.

_____

Keith P. Sanford, Ph.D.

_____

Shawn J. Latendresse, Ph.D.

_____

David K. Pooler, Ph.D.

Accepted by the Graduate School

August 2018

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J. Larry Lyon, Ph.D., Dean

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ACKNOWLEDGMENTS

I would like to express immense gratitude to my faculty mentor and dissertation advisor, Dr. Sara Dolan, for her guidance and support throughout the dissertation process and my graduate school career. My completion of this project and my persistence throughout graduate school would not have been possible without her continual encouragement, compassion, confidence in my abilities, and incredible wealth of knowledge. I would also like to thank my committee members: Dr. Jim Patton, Dr. Keith Sanford, Dr. Shawn Latendresse, and Dr. David Pooler, for their insightful contributions and thoughtful discussion. Additionally, I would like to thank Dr. Annie Ginty for lending her expertise and consultation, as well as her equipment, in the completion of this project. I would especially like to thank the staff and residents of Cenikor Foundation, Waco and Christian Farms-Treehouse, Inc. for welcoming my presence and supporting alcohol use research. To my fellow graduate students and cohort members, thank you for your solidarity as we faced challenges together and for your genuine friendship, which I continue to cherish. To my parents, thank you for your unconditional love and for instilling in me the values of passion, hard work, and perseverance- none of my achievements would be possible without you. To my uncle, thank you for your encouragement when it was needed most. Finally, to my fiancé, Danny, I love you and I thank you for being the calm in the storm.

For Samuel L'Esperance and Taylor Chenail

May my commitment to serving others honor your memory

CHAPTER ONE

Introduction

Clinical Significance of Alcohol Use Disorder

This study explored a possible mechanism of relapse in individuals with alcohol use disorder (AUD). AUD as defined by the Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition (DSM-5) represents a grave public health concern in the U.S., with the most recent National Epidemiological Survey on Alcohol and Related Conditions (NESARC) estimating a 12-month prevalence rate of 13.9% and lifetime prevalence of 29.1% in adults over 18 (American Psychiatric Association, 2013; Grant et al., 2015). AUD also represents a significant global health problem, with epidemiological studies in countries across the globe reflecting similarly high prevalence estimates (de Graaf, Have, van Gool, & van Dorsselaer, 2011; Teesson et al., 2010). The World Health Organization (WHO; 2008) has estimated that global 12-month prevalence rates of AUD in individuals aged 15 and older range from 0-16%, with the highest prevalence rates in Eastern European countries.

The high prevalence of AUD contributes significantly to the global burden of disease. AUD is considered the fourth-most disabling disease category in low- to middle-income countries, and the third-most disabling in high-income countries (Rehm, 2011). Further, the WHO Global Status Report on Alcohol and Health (2014) reported that in 2012, 5.1% of the global burden of disease and injury was attributable to alcohol consumption, as well as 5.9% of all global deaths. Problematic alcohol use is considered

a significant contributing factor to ischemic heart disease, stroke, road injury, and hypertensive heart disease, which are the first, second, ninth, and tenth leading causes of death worldwide, respectively (WHO, 2014). The associations between AUD and disability and morbidity also contribute to the significant economic costs of heavy alcohol use. The estimated cost of excessive drinking in the U.S. in 2010 was $249 billion, with the distribution of total cost percentage consisting of lost productivity (71.9%), healthcare (11.4%), and other costs (16.7%) (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015).

AUD is also associated with significant negative outcomes for the individual. Heavy alcohol use has been associated with increased risk for unintentional physical injuries, victimization from sexual assault, aggressive behavior, intimate partner violence, child abuse, and suicidality (Bácskai, Czobor, & Gerevich, 2008; Gmel & Rhem, 2003; Klimkiewicz, Klimkiewicz, Jakubczyk, Kieres-Salomonski, & Wojnar, 2015; Pedrelli, Collado, Shapero, Brill, & MacPherson, 2016). Additionally, heavy alcohol use is associated with drinking and driving, legal problems, antisocial behavior, tobacco smoking, and illicit drug use (Button et al., 2007; Kraus, Baumeister, Pabst, & Orth, 2009; Pedrelli et al., 2016; Wechsler, Lee, Nelson, & Kuo, 2002). Academic difficulties and decreased work productivity have also been associated with problematic alcohol use, as well as increased interpersonal conflicts (Gmel & Rhem, 2003; Kraus et al., 2009; Pedrelli et al., 2016; Wechsler et al., 2002). Alcohol dependence is associated with high psychiatric comorbidity (Blanco et al., 2013; Button et al., 2007; Jacobsen, Southwick, & Kosten, 2001; Klimkiewicz et al., 2015; Kushner et al., 2005; Miller, Klamen, Hoffman, & Flaherty, 1996; Ohlmeier et al., 2008; Sánchez-Peña, Alvarez-Cotoli, & Rodríguez-

Solano, 2012), with estimated 12-month comorbidity rates of 27.9% with major depressive disorder, 1.9% with bipolar disorder, 36.9% with anxiety disorders, and 7.7% with posttraumatic stress disorder (Kessler et al., 1996), as well as a lifetime comorbidity rate of 24% with schizophrenia (Regier et al., 1990). These comorbidities have been associated with increased severity of AUD symptoms (Blanco et al., 2013; Brière, Rohde, Seeley, Klein, & Lewinsohn, 2014; Eddie, Hunter-Reel, Epstein, & Cohn, 2015; Sells et al., 2016) and higher rates of alcohol relapse (Kushner et al., 2005; Lynskey, 1998) and treatment seeking (Blanco et al., 2013; Brady, Back, & Coffey, 2004; Lynskey, 1998).

Despite the high prevalence of AUD and the severity of associated psychosocial and health risks, the rates of individuals with AUD who receive treatment remain low. The Substance Abuse and Mental Health Services Administration (SAMHSA; 2015) reported that in 2014, only 7.6% of individuals ages 12 and older with DSM-IV alcohol dependence or abuse received treatment for their alcohol use in the past year, and AUD research in other nations reports similarly low rates of treatment (Lea, Reynolds, & Wit, 2013; Probst, Manthey, Martinez, & Rehm, 2015; Teesson et al., 2010). However, the literature would suggest that individuals with AUD who receive treatment represent a population with greater severity of AUD symptomatology and related problems (Cohen, Feinn, Arias, & Kranzler, 2007; Ko, Martins, Kuramoto, & Chilcoat, 2010; Kuramoto, Martins, Ko, & Chilcoat, 2011; Mojtabai & Singh, 2007; Saunders, Zygowicz, & D'Angelo, 2006; Weisner, Matzger, Tam, & Schmidt, 2002), and by extension, higher risk for relapse.

AUD has long been defined as a chronic, relapsing disorder (Brandon, Vidrine, & Litvin, 2007; Brownell, Marlatt, Lichtenstein, & Wilson, 1986; Koob & Volkow, 2010;

Institute of Medicine, 1998; McLellan, Lewis, O'Brien, & Kleber, 2000; Miller, Westerberg, Harris, & Tonigan, 1996; Seo et al., 2013; Sinha, 2008), with higher rates of relapse[1] associated with a more severe symptom presentation (de Bruijn, van den Brink, de Graaf, & Vollebergh, 2006; Institute of Medicine, 1998; Miller et al., 1996; Tuithof, ten Have, van den Brink, Vollebergh, & de Graaf, 2014). Dawson, Goldstein, and Grant (2007) report that individuals who receive AUD treatment have a higher relapse rate compared to those who do not receive treatment, and reviews of the literature in clinical populations with AUD reflect high relapse rates, between 40 and 92% (Brandon et al., 2007; McLellan et al., 2000), depending on study design (Moos & Moos, 2006a; Moos & Moos, 2006b). Moos & Moos (2006a, 2006b) may have demonstrated lower relapse rates due to the longitudinal nature of a 16-year follow-up, which may have reflected behavioral change occurring over time not due to treatment effects. Higher relapse rates may be reflective of the shorter follow-up periods of other studies (Brandon et al., 2007; Dawson et al., 2007; McLellan et al., 2000), which are suggestive of symptom persistence despite treatment. The severe financial, physical and mental health, psychosocial, and legal costs incurred by AUD, coupled with the high prevalence and relapse rates associated with the disorder, highlight the societal and clinical importance of continued study of the mechanisms that maintain AUD and its accompanying relapses.

Relapse and Cue Reactivity

Reactivity to alcohol cues has been investigated as a mechanism for AUD relapse. Cue reactivity refers to changes observed in response to alcohol cues (e.g. the smell of alcohol, a photo of a person drinking an alcoholic beverage), including changes in brain

[1] Relapse can be defined as a return to alcohol use following a period of abstinence (Barrick & Connors, 2002; Garland, Franken, & Howard, 2011; Miller et al., 1996; Moos & Moos, 2006a).

activation patterns, changes in physiological responses typically controlled by the autonomic nervous system such as heart rate and skin conductance, and changes in self-reported craving, or desire for alcohol (Carter & Tiffany, 1999; Childress et al., 1993; Drummond, 2000). Cues may include: external experiences, such as visual or olfactory stimuli; internal experiences, including affective states or cognitions; or associations made between stimuli, such as stimuli that are temporally proximal to alcohol use behaviors or stimuli that occur in a particular order before alcohol use (Drummond, 2000; Litt, Cooney, Kadden, & Gaupp, 1990). Cue reactivity is described within the context of classical conditioning theory due to the reliable pairing of certain stimuli (e.g. the sight of a whiskey bottle) and alcohol use, in which repeated pairing of the unconditioned stimulus and unconditioned response results in conditioned responses (e.g. increased heart rate) to conditioned stimuli (e.g. the sight of a whiskey bottle) (Carter & Tiffany, 1999; Koob & Volkow, 2010; Monti et al., 1987; Stasiewicz, Brandon, & Bradizza, 2007).

Various conditioning theories have been suggested in the explanation of substance cue reactivity. Wikler (1948) proposed that a withdrawal state occurs in alcohol-dependent patients when alcohol is not consumed after the presentation of alcohol cues, resulting in cue reactivity via conditioned physiological states of withdrawal. Siegel (1975) has offered an alternative explanation, arguing that cue reactivity represents a conditioned state of compensatory physiological response in contrast to the drug effect, corresponding to increased arousal (e.g., increased heart rate) in compensation for the depressant effects of alcohol. The literature suggests that a third model, the conditioned appetitive-motivational model (Stewart, de Wit, & Eikelboom, 1984), has the most

empirical support in the explanation of cue reactivity processes (Carter & Tiffany, 1999; Monti, Kadden, Rohsenow, Cooney, & Abrams, 2002; Niaura et al., 1988; Rohsenow et al., 1992; Vollstädt-Klein et al., 2011; Witteman et al., 2015). In contrast to Wikler's (1948) and Siegel's (1975) models of cue reactivity, the appetitive-motivational model posits that drug-relevant stimuli become conditioned stimuli that elicit an incentive-motivational state, which produces physiological responses consistent with enhanced drug-taking motivation (Stewart et al., 1984). According to this model, the intensity of response to drug-relevant cues varies with the salience of the cue, and salience is influenced by cue characteristics, individual factors, contextual factors, and neural sensitization processes occurring over the course of chronic drug use (Drummond, 2000; Robinson & Berridge, 1993; Robinson & Berridge, 2000; Robinson & Berridge, 2001).

The literature suggests that individuals with a longer duration of alcohol dependence exhibit greater reactivity to alcohol cues, including increased skin conductance, heart rate variability (Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Kaplan et al., 1985), and activation of motivational brain pathways (e.g., anterior cingulate cortex, orbitofrontal cortex; Myrick et al., 2003; Sjoerds, van den Brink, Beekman, Penninx, & Veltman, 2014). Additionally, cues related to participants' alcoholic beverage of choice, as opposed to a non-preferential drink, resulted in the greatest physiological cue reactivity and subjective craving (Staiger & White, 1991), suggesting that alcohol cues with high personal salience elicit the greatest reactivity. Greater physiological cue reactivity is also associated with increased subjective alcohol craving (Cooney et al., 1997; Glautier & Drummond, 1994; Kaplan et al., 1985; Myrick et al., 2003; Sjoerds et al., 2014, Witteman et al., 2015). While self-reported craving is not

consistently correlated with increased relapse rate, with some studies suggesting a positive correlation (Cooney et al., 1997; Higley et al., 2011; Monti, Rohsenow, & Hutchison, 2000; Sjoerds et al., 2014) and others suggesting a lack thereof (Koob & Volkow, 2010, Witteman et al., 2015), research has established an association between increased cue reactivity and shorter time to alcohol relapse (Cooney et al., 1997; Monti et al., 2000). These findings emphasize the importance of cue reactivity in relapse risk for clinical AUD populations.

Cue reactivity represents a challenge for individuals with AUD in the community, who may experience marked difficulty abstaining from alcohol use when faced with alcohol cues. Individuals with AUD frequently face high urge[2] situations involving the presence of alcohol cues in everyday life (e.g., eating in a restaurant where others are drinking alcohol, watching television when commercials for alcoholic beverages are presented), and subjective and objective reactivity to those cues poses a significant challenge in maintaining sobriety.

Working Memory Impairment in AUD

A possible explanatory factor for the persistence of AUD and high relapse rates is the experience of neuropsychological deficits, particularly working memory impairment, which may result in difficulty recalling and using coping skills during a high urge situation. Working memory has been defined as a multi-faceted and limited-capacity cognitive system that temporarily stores information and supports thought processes by providing an interface between perception, long-term memory, and behavioral action (Baddeley, 2003; Baddeley, 2012). Baddeley & Hitch (1974) have proposed a model of

[2] The definitions of "urge" and "craving" overlap and the terms are henceforth used interchangeably.

working memory that reflects its complexity, with a three-part structure comprised of: the phonological loop, which processes sound and language; the visuospatial sketchpad, which processes visual and spatial information; and the central executive, a control system with limited attentional capacity. The neurotoxic effects of alcohol have implications for working memory ability as outlined by Baddeley & Hitch (1974) after chronic alcohol use. The literature suggests that chronic alcohol use results in significant neurotoxic effects impacting cognitive performance, including resultant deficits in domains utilizing the three-part structure of working memory, such as visual-spatial tasks and tests of executive functioning and working memory capacity (Brust, 2010; Guerri & Pascual, 2010; Harper, 2007).

It has been estimated that 50-80% of individuals with AUD have mild to severe neurocognitive impairment (Bates, Bowden, & Barry, 2002; Bernardin, Maheut-Bosser, & Paille, 2014; Fein, Bachman, Fisher, & Davenport, 1990). Structural and functional brain imaging studies with individuals with AUD have revealed decreased connectivity in the corpus callosum (Konrad et al., 2012) and reduced gray and white matter volume in a variety of brain areas, including striatal structures, such as the caudate nucleus and putamen (Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005), and frontal lobe structures, including the prefrontal and anterior cingulate cortices (Harper, Dixon, Sheedy, & Garrick, 2003; Kubota et al., 2001; Liu, Matochik, Cadet, & London, 1998; Medina et al., 2008; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Rando et al., 2011). Research has also shown altered brain activity in the frontal cortex of individuals with AUD (Blaine, Seo, & Sinha, 2015; Campanella et al., 2013; George, Potts, Kothman, Martin, & Mukundan, 2004; Goldstein & Volkow, 2002; Harper et al., 2003;

Schweinsburg et al., 2001; Sullivan et al., 2003), where complex working memory abilities, such as attending to relevant stimuli and performing executive functions to process sensory input, are mediated (Courtney, Petit, Haxby, & Ungerleider, 1998; Curtis & D'Esposito, 2003; D'Esposito, 2007; Lara & Wallis, 2015; Nee et al., 2013; Postle, 2006; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000, Rottschy et al., 2012).

The bulk of the literature demonstrates that individuals with AUD, including those currently drinking, those recently engaged in detoxification treatment, and those with years of sobriety, exhibit deficits in working memory task performance as compared to healthy controls (Ambrose, Bowden, & Whelan, 2001; Bechara & Martin, 2004; Cunha & Novaes, 2004; Kopera et al., 2012; Oscar-Berman, Kirkley, Gansler, & Couture, 2004; Ratti, Bo, Giardini, & Soragna, 2002; Stavro, Pelletier, & Potvin, 2013; Tapert et al., 2001), though some studies show conflicting results (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011; Desmond et al., 2003; Pfefferbaum et al., 2001). These conflicting results may be partially explained by literature suggesting that individuals with AUD do not demonstrate reduced working memory span and have similar direct recall ability to healthy controls, but show reduced working memory performance on more complex working memory tasks, such as alphabetical or sequential recall (Noël et al., 2001). As a result, the present study utilized a measure of complex working memory ability.

Working Memory Impairment and AUD Treatment Outcome

Impairment in working memory has significant implications for the effectiveness of AUD treatment. There is research suggesting that neuropsychological deficits often spontaneously recover over time with abstinence from alcohol (Gould, 2010; Noël, Van

Der Linden, & Bechara, 2006); however, many individuals with AUD enter treatment directly following detoxification from alcohol and do not experience the benefits of such recovery until later in treatment or even after discharge. By extension, working memory deficits have demonstrated a negative impact on AUD treatment and outcomes, including impaired ability to learn novel concepts in treatment (Pitel et al., 2007) and increased risk of alcohol relapse post-treatment (Noël et al., 2002). While findings are mixed regarding a direct link between impaired neuropsychological functioning and negative AUD treatment outcome (Bates, Buckman, & Nguyen, 2013; Morgenstern & Bates, 1999), current literature is suggestive of an indirect but vitally important relationship that has yet to be clarified. Bates et al. (2002) have put forth alternative models for the relationship between neuropsychological impairment and substance use treatment outcome that include possible mediation or moderation relationships, and more recent research has found support for both mediation and moderation models that include the influences of factors such as impulsivity and self-efficacy (Bates, Pawlak, Tonigan, & Buckman, 2006; Gunn & Finn, 2013; Khurana et al., 2013). Overall, the literature would suggest that working memory deficits represent a barrier to potential treatment benefit and outcome, likely due to indirect, negative effects on treatment.

Research results demonstrating less efficient and more cognitively taxing learning processes (Fama, Pfefferbaum, & Sullivan, 2004) imply that individuals with AUD may have marked difficulty learning new coping skills in treatment. Further, demonstration that individuals with AUD scoring below median cognitive function show significantly less coping skill acquisition as compared to those with higher cognitive function (Kiluk, Nich, & Carroll, 2011) suggests that neurocognitive impairment may hinder the learning

of coping skills during treatment. Working memory impairment may thus affect treatment outcome by inhibiting the adequate understanding and learning of coping skills during treatment. The present study sought to demonstrate the effect of alcohol cue exposure on working memory performance to establish a possible pathway by which coping skill acquisition is impaired in individuals with AUD.

Working Memory and Cue Reactivity

Working memory ability may also have implications for the management of coping response when faced with alcohol cues during high relapse risk situations. Results from functional magnetic resonance imaging (fMRI) research examining brain response to alcohol cues have shown that brain areas activated during cue exposure overlap with areas implicated in complex working memory. The dorsolateral prefrontal cortex (DLPFC), a brain area implicated in working memory (Curtis & D'Esposito, 2003; Levy & Goldman-Rakic, 2000; Petrides, 2000), shows activation during the presentation of alcohol cues for individuals with AUD (Goldstein & Volkow, 2002, 2011; Wilson, Sayette, & Fiez, 2004; Wrase et al., 2002). Further, research with healthy participants has shown that induced stress results in decreased DLPFC activation during a working memory task (Qin, Hermans, van Marle, Luo, & Fernández, 2009) and impaired working memory performance (Oei, Everaerd, Elzinga, van Well, & Bermond, 2006; Qin et al., 2009; Schoofs, Preuβ, & Wolf, 2008; Schoofs, Wolf, & Smeets, 2009; Shields, Sazma, & Yonelinas, 2016), with particular impairment shown during complex working memory tasks requiring verbal manipulation of information or alphabetical or sequential recall (Oei et al., 2006; Shields et al., 2016). Evidence that transcranial direct stimulation of the DLPFC both reduces cue reactivity and alcohol craving in individuals with AUD

(Wietschorke, Lippold, Jacob, Polak, & Herrmann, 2016) and improves stress-induced working memory impairment in healthy participants (Bogdanov & Schwabe, 2016) offers preliminary support for a causal relationship between DLPFC activation and cue reactivity/craving in individuals with AUD, as well as between DLPFC activation and working memory ability. The implication of DLPFC involvement in working memory and alcohol cue reactivity, as well as the differential activation and impaired working memory task performance noted in healthy participants under stress, would suggest that alcohol cues may have a detrimental effect on cognitive processing during tasks involving working memory.

The literature also indicates that individuals with AUD experience an enhanced craving state of increased anxiety, negative emotion, systolic blood pressure, and cortisol levels in response to alcohol-cue exposures (Fox, Bergquist, Hong, & Sinha, 2007; Sinha, 2011, 2012; Sinha et al., 2009; Thomas, Bacon, Sinha, Uhart, & Adinoff, 2012). These results suggest that alcohol cue exposure elicits similar responses in individuals with AUD to the responses that stress induction elicits in healthy individuals, which include increased negative affect (Qin et al., 2009; Schoofs et al., 2008), heart rate (Qin et al., 2009), and cortisol levels (Oei et al., 2006; Qin et al., 2009; Schoofs et al., 2008; Schoofs et al., 2009). Alcohol cues may therefore have similarly impairing effects on working memory as stress induction has had on working memory performance in healthy participants.

Physiological Measures of Cue Reactivity

A number of studies have documented increases in blood pressure (Sinha et al., 2009) and heart rate (Carter & Tiffany, 1999; Cooney et al., 1997; Kaplan et al., 1985;

Niaura et al., 1988; Sinha et al., 2009; Staiger & White, 1991) for individuals with AUD during alcohol cue exposure paradigms, while other studies have failed to find significant cardiovascular increases (Fox et al., 2007; Litt et al., 1990; Reid, Flammino, Starosta, Palamar, & Franck, 2006). Additionally, investigation of physiological responses to stress tasks in individuals with AUD has demonstrated mixed results, with some studies demonstrating significant increases in blood pressure and heart rate during stress tasks (Maisto, Ewart, Connors, Funderburk, & Krenek, 2009) and others reflecting attenuated cardiovascular responses (Panknin, Dickensheets, Nixon, & Lavallo, 2002; Thomas, Randall, Brady, See, & Drobes, 2011). Given the mixed findings in the literature regarding evidence of physiological arousal during alcohol cue exposure and other tasks designed to evoke heightened arousal, the current study assessed heart rate and systolic and diastolic blood pressure throughout the study protocol to further explore physiological cue reactivity in individuals with AUD. The current study utilized an imaginal alcohol cue exposure procedure similar to that used in a study conducted by Sinha et al. (2009), in which individuals with AUD in residential treatment underwent stress-, alcohol-, and neutral-cue exposures to assess cardiovascular response and subjective experience of craving, distress, and negative emotion as a result of the cues. Sinha et al. (2009) found significant increases in systolic blood pressure and heart rate at the time of alcohol cue exposure, as well as subjective distress, alcohol craving, and negative emotion; given the similarity in methodology, significant increases in systolic blood pressure and heart rate during alcohol cue exposure were hypothesized in the current study.

Theoretical Mechanism of Working Memory Impairment and Alcohol Cues

The current study hypothesized that alcohol cue exposure would have a detrimental effect on working memory ability in individuals with AUD, which may have negative implications for later coping with high-risk situations. Dual-process models of substance use further elucidate a possible theoretical mechanism in this relationship, and state that decisions to engage in substance use behavior are influenced by both reflective, top-down processes that are largely controlled by the prefrontal cortex, and impulsive, bottom-up processes that are controlled by the amygdala and automatic associations with pleasure and reward formed through learning (Bechara, 2005; Friese, Gianotti, & Knoch, 2016; Hofmann, Friese, & Wiers, 2008; Stevenson, Dvorak, Kuvaas, Williams, & Spaeth, 2015; Tahaney, Kantner, & Palfai, 2014; Wiers, Ames, Hofmann, Krank, & Stacy, 2010).

In a chronic, relapsing substance use population, bottom-up processing ruled by automatic responding is thought to override top-down processing, in part, due to neurocognitive deficits in the prefrontal cortex that weaken reflective processes (Noël et al., 2006; Noël, Brevers, & Bechara, 2013). Literature investigating these neurocognitive processes in substance use populations has demonstrated poor performance on the Iowa Gambling Task (Andó et al., 2012; Barry & Petry, 2008; De Wilde, Verdejo-García, Sabbe, Hulstijn, & Dom, 2013; Le Berre et al., 2014; van Toor et al., 2011), a measure that assesses decision-making ability, with worse performance in those individuals with more severe working memory deficits (Brevers et al., 2014; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). These results suggest that impairment in higher-order cognitive processes may play a role in an individual's ability to use top-down processes involving cognitive control, resulting in the stronger influence of bottom-up, automatic

processes on behavioral response, and by extension, decreased ability to access and use coping skills.

The present study aimed to investigate complex working memory ability in the context of alcohol cue exposure, such that alcohol cue exposure was hypothesized to correlate with subjective reports of distress and alcohol craving as well as cardiovascular measures. Additionally, participants in the alcohol-cue group were hypothesized to exhibit attenuated improvement in working memory ability after cue exposure as compared to the neutral-cue group. Complex working memory ability was measured using a verbal (letter-stimuli) n-back task, which tests an individual's ability to process and manipulate verbal information to respond to changing contextual demands (Baddeley, 2003), and has been found to be impaired in individuals with AUD (Marx, Krause, Berger, & Häßler, 2014; Stavro et al., 2013).

The current study utilized exposure to alcohol cues to induce cue reactivity and to examine the effects of cue reactivity on the n-back task. Imaginal cue exposure was used, as imaginal cue exposure techniques have shown effectiveness in inducing cue reactivity and alcohol craving with both general (Erblich, Montgomery, & Bovbjerg, 2009) and personalized (Fox et al., 2007; Payne et al., 1992; Rohsenow, 2013; Sinha et al., 2009) alcohol scripts. Personalized imagery scripts were used in the present study, based upon results showing that personalized alcohol scripts produced increases in alcohol craving and anxiety lasting up to 30 minutes post-cue exposure (Fox et al., 2007; Sinha et al., 2009), conditions under which performance on a test of working memory is likely to be challenged. Imaginal alcohol cue exposure allows researchers to mimic encounters with high-risk relapse situations in a laboratory setting.

Significance of the Present Study

The proposed study examined the effect of alcohol cue exposure on working memory, subjective distress, and alcohol craving using a repeated-measures design, in which each construct was assessed both before and after an individualized, imaginal cue exposure. Cardiovascular responses, specifically blood pressure and heart rate, were also measured at various times throughout the study protocol. Individuals in inpatient treatment for AUD participated in the study, with two groups undergoing either an alcohol- or neutral-cue exposure.

The current study offers insight into a possible mechanism of AUD relapse that has not yet been extensively explored. The literature has demonstrated that stress induction results in increased negative emotion and working memory impairment in healthy participants (Oei et al., 2006; Qin et al., 2009; Schoofs et al., 2008; Schoofs et al., 2009; Shields et al., 2016), but research has not shown how stress induction, in the form of alcohol cue exposure, may affect working memory in a clinical AUD population. Additionally, the extant literature has established that individuals with AUD exhibit reactivity to alcohol cues in the form of increased alcohol craving and negative emotion (Erblich et al., 2009; Fox et al., 2007; Payne et al., 1992; Rohsenow, 2013; Sinha et al., 2009; Sinha, 2011, 2012; Thomas et al., 2012) and that working memory is impaired in individuals with AUD (Ambrose et al., 2001; Bechara & Martin, 2004; Cunha & Novaes, 2004; Kopera et al., 2012; Oscar-Berman et al., 2004; Ratti et al., 2002; Stavro et al., 2013; Tapert et al., 2001), but subjective reactivity to alcohol cues has not been examined in relation to working memory performance in a clinical AUD population. Finally, mixed findings regarding cardiovascular responses of individuals with AUD to alcohol

cue exposure (Carter & Tiffany, 1999; Cooney et al., 1997; Fox et al., 2007; Kaplan et al., 1985; Litt et al., 1990; Niaura et al., 1988; Reid et al., 2006; Sinha et al., 2009; Staiger & White, 1991) and stress tasks (Maisto et al., 2009; Panknin et al., 2002; Thomas et al., 2011) warrant further study of physiological cue reactivity. This study investigated alcohol cue reactivity, in the form of subjective reports of distress and alcohol craving as well as objective blood pressure and heart rate responses, and the change in working memory performance that may result from exposure to alcohol cues.

The literature suggests that neurocognitive impairment may have a negative effect on relapse in AUD (Bates et al., 2002; Noël et al., 2002; Pitel et al., 2007), but has not elucidated the mechanism by which neurocognitive impairment negatively affects outcome. The current study is the first of its kind known to the author to investigate working memory and subjective and objective cue reactivity in a clinical AUD population both before and after an alcohol cue exposure to detect performance differences based upon response to the cues. This study may shed light on the correlation between working memory and distress resulting from exposure to alcohol cues, an association that should be considered in the treatment of individuals with AUD due to the ubiquitous nature of alcohol cues outside of the treatment environment.

Study Hypotheses

H.1: Participants in the alcohol-cue condition will achieve significantly lesser improvement in working memory than those in the neutral-cue condition following a cue exposure.

H.2: The difference between pre- and post-cue working memory scores will be negatively correlated with the differences between pre- and post-cue subjective distress and alcohol craving scores in the alcohol- and neutral-cue conditions.

H.3: Systolic blood pressure and heart rate will increase significantly during cue exposure for the alcohol-cue condition and will not change significantly during cue exposure for the neutral-cue condition.

CHAPTER TWO

Method

Participants

The sample included 91 individuals (see power analysis below) attending inpatient substance use treatment in central Texas. Patients in two residential treatment centers were recruited for participation in the study. Treatment in these facilities included individual and group counseling, chemical dependency education, 12-step meetings, relapse prevention, aftercare planning, and classes for parenting, anger management, and life skills. Participants were recruited from inpatient therapy groups. Residents at each facility were given a brief synopsis of the study at the beginning of a group therapy session and had the opportunity to make an appointment for study participation.

Upon completion of informed consent, individuals were randomly assigned to one of two groups, with 46 participants assigned to the neutral-cue group and 45 assigned to the alcohol-cue group. Random assignment was conducted using the randomization tool in Qualtrics. Residents were included in the sample if they had a diagnosis of alcohol use disorder, were currently stable on psychotropic or analgesic medications, and had been abstinent from alcohol use for at least 7 days. Exclusion criteria were: current experience of psychosis, mania, or substance withdrawal symptoms; history of non-substance-related psychotic or manic episodes; severe substance use disorder other than alcohol use

disorder; prescription of or change in dose of psychiatric or pain medications less than 1 month prior to protocol administration; and age under 18 or over 60.

The proposed sample size was 60 participants and was determined by conducting a power analysis using the G*Power program (Faul, Erdfelder, Lang, & Buchner, 2007). The effect size from research conducted by Cox, Yeates, & Regan (1999) was used to predict an adequate sample size for the current study. Cox et al. (1999) explored response time differences in heavy and light drinkers using an emotional Stroop task with alcohol-related stimuli. This study resembled the proposed research method in its exploration of differential neuropsychological response based upon alcohol cue exposure. The G*Power program determined that 58 participants is an adequate sample for the proposed study to achieve power of .80 and a .971 Cohen's *d* effect size. Additionally, Fox et al. (2007) studied the effect of imaginal alcohol cue exposure on self-reported anxiety and alcohol craving in 20 subjects with AUD, and reported similarly large effects. Finally, a meta-analysis of the effects of acute stress on core executive functions in healthy subjects reported a Hedges' *g* of .519 for the effect of stress on working memory after controlling for other moderators, and noted that a sample size of 60 (one-tailed test) would be required to detect such an effect with power of .80 (Shields et al., 2016). The compilation of the results of these studies and the formal power analysis supported the proposed sample size. Additional participants were included in the study with the intention of increasing power; however, given that observed power is estimated based upon effect size and the current study yielded few statistically significant findings with only small effect sizes, the goal of increased power was not achieved.

Procedure

The Principal Investigator provided verbal explanation of the study procedures and prompted potential participants to read the consent form completely. Participants demonstrated understanding of the implications of participation via a verbal summary to the Principal Investigator, and verbal consent for participation was obtained in accordance with the waiver of written consent provided by the Baylor University Institutional Review Board in order to protect the confidentiality of research participants. Demographic information and inclusion/exclusion criteria were assessed with a questionnaire administered via Qualtrics, and those who did not meet criteria for the study were thanked for their time and provided with an excused absence for any missed treatment programming. Baseline measures assessed the presence of a diagnosis of AUD, overall distress level, alcohol craving, and working memory. Systolic and diastolic blood pressure and heart rate were measured with an automatic sphygmomanometer cuffed on the participant's non-dominant arm at 28 time points throughout the entirety of the study protocol, including measurements during baseline, initial working memory, cue exposure, and post-cue working memory time points. After completion of baseline measures, participants were guided through an imaginal cue exposure task, with the experimental group using alcohol-related cues (i.e. a recent instance of alcohol use) and the control group using neutral cues (i.e. a recent relaxing situation). Working memory, overall distress level, and alcohol craving were re-assessed post-cue exposure. Participants with post-cue overall distress or alcohol craving scores above their baseline scores were guided through an urge surfing coping task to lower distress and craving to at or below baseline report.

Measures

Demographics/Inclusion/Exclusion Criteria Assessment Form. A 13-item self-report form created by the Principal Investigator for the purposes of this study was used to inquire about the participant's age, gender, race, ethnicity, length of time in treatment, history of substance use treatment, history of psychiatric symptoms and diagnoses, use of prescribed psychiatric medications and changes in the last month, use of alcohol in the past 7 days, past experience of alcohol craving, and current experience of withdrawal symptoms related to alcohol use. Eligibility to participate in the study was determined based on responses to the questionnaire.

Mini-International Neuropsychiatric Interview- Plus 5.0.0 (Sheehan et al., 1997). The Mini-International Neuropsychiatric Interview-Plus 5.0.0 (M.I.N.I.-Plus) was used to assess the presence of psychotic, manic, and substance use disorder symptoms. The M.I.N.I.-Plus is a structured diagnostic interview used to determine if research participants and patients in clinical settings meet diagnostic criteria for mental health disorders. The Psychotic Disorders and Manic Episode modules were administered to assess the current experience of psychotic or manic symptoms. The Alcohol Abuse and Dependence and Non-Alcohol Psychoactive Substance Use Disorders modules were administered to confirm substance use disorder diagnoses. The M.I.N.I.-Plus is characterized by good to very good validity, evidenced by strong concordance rates with Structured Clinical Interview for DSM-III-R Patients (SCID-P) diagnoses of current mania ($\kappa = .67$), current psychotic disorder ($\kappa = .53$), current alcohol dependence ($\kappa = .67$), and current drug dependence ($\kappa = .43$) (Sheehan et al., 1997). The M.I.N.I.-Plus

also demonstrates high concordance with diagnoses on the Composite International Diagnostic Interview (CIDI) of current manic episode (κ = .65), current psychotic symptoms (κ = 76), alcohol dependence (κ = .82), and drug dependence (κ = .81) (Lecrubier et al., 1997). The M.I.N.I.-Plus demonstrates adequate reliability for the diagnoses of current mania (inter-rater κ = .79; test-retest κ = .35), current psychotic disorder (inter-rater κ = .81; test-retest κ = .77), current alcohol dependence (inter-rater κ = 1.00; test-retest κ = .86), and current drug dependence (inter-rater κ = .91; test-retest κ = .96) (Sheehan et al., 1997).

Subjective Units of Distress Scale (SUDS). Participants were asked to rate his or her level of distress on a Subjective Units of Distress Scale (SUDS) at baseline and directly following the imaginal alcohol cue exposure. The SUDS measurement asks participants to rate, on a scale of 0-100, how much anxiety or discomfort they feel in the moment. The scale utilizes the following anchors: 0, no anxiety or discomfort at all; 25, slight anxiety or discomfort; 50, moderate anxiety or discomfort; 75, high anxiety or discomfort; and 100, extreme anxiety or discomfort.

Alcohol Craving Rating Scale. Participants were asked to rate his or her level of alcohol craving at baseline and directly following the post-cue exposure SUDS. The scale asks participants to rate, on a scale of 0-100, the degree to which he or she is craving an alcoholic drink in the moment. The scale utilizes the following anchors: 0, no craving at all; 25, slight craving; 50, moderate craving; 75, high craving; and 100, extreme craving.

Alcohol Craving Questionnaire- Short Form- Revised (Singleton, Tiffany, & Henningfield, 2004). The Alcohol Craving Questionnaire- Short Form- Revised (ACQ-SF-R) was used to assess acute alcohol craving at baseline and directly following the post-cue exposure Alcohol Craving Rating Scale. The ACQ-SF-R is a 12-item, self-report questionnaire used to assess current alcohol craving. It is a shortened version of the 47-item Alcohol Craving Questionnaire (ACQ-NOW), and contains 12 items strongly correlated with its four subscales and total ACQ score (Singleton, 1999; Tiffany, Carter, & Singleton, 2000). The validity of the ACQ-NOW has been established by studies showing strong, positive correlations with other validated measures of alcohol craving, such as the Desires for Alcohol Questionnaire (Love, James & Willner, 1998) and the Obsessive Compulsive Drinking Scale (Anton, Moak, & Latham, 1995; Preuss, Schutz, Koch, & Soyka, 1998a), as well as related constructs, including number of drinking days in the past month and anger and frustration (Douglas, Singleton, & Henningfield, 1995). The four subscales include: compulsivity, or urge/desire to drink in anticipation of loss of control over drinking; expectancy, or urge/desire to drink in anticipation of the positive benefits of drinking; purposefulness, or urge/desire to drink coupled with intent or planning to drink; and emotionality, or urge/desire to drink in anticipation of relief from negative affect. The estimated standardized alpha coefficients for the subscales range from .77 to .86 (Singleton et al., 2004). The ACQ-SF-R demonstrated good internal consistency in the current study for both pre-cue ($\alpha = .81$) and post-cue ($\alpha = .84$) measurements.

Letter Stimuli N-Back Task (Jaeggi et al., 2010). A computer-administered, letter-stimuli n-back task was used to assess participant working memory pre- and post-

cue exposure. The n-back task was administered via the Inquisit 3 software package on a laptop computer. Participants and Principal Investigator read the instruction pages at the beginning of the task together prior to commencement of the practice trials, and participants had the opportunity to ask questions about the task. The n-back task includes 0-, 1-, and 2-back levels, with a practice trial for each n-back level. During the 0-back task, a target letter is identified in the first stimulus of the trial; during the trial, letters appear sequentially and the participant must press "A" on the keyboard when the target letter is displayed. During the 1- and 2-back tasks, each trial sequentially displays letters and asks the participant to press "A" on the keyboard when the stimulus matches the letter displayed 1 or 2 stimuli before, respectively. Participants received feedback at the end of each practice trial about accuracy in the form of percentage of accurate stimulus responses. Participants did not receive feedback about accuracy during the task. There are three trials of each level during the task, for a total of 9 trials. The trials are administered in random order. Participants were asked to complete all 9 trials of the task in each administration. The n-back task has demonstrated adequate reliability, with a Cronbach's α of .79 (Jaeggi et al., 2010). In the current study, the n-back task demonstrated good internal consistency for both pre-cue (α = .81) and post-cue (α = .79) measurements.

Scene Construction Questionnaire (Sinha & Tuit, 2012). The Scene Construction Questionnaire (SCQ) was administered to guide the imaginal cue exposure. Participants in this study were randomly assigned to the alcohol-cue SCQ group, in which they described a situation resulting in a desire for and consumption of alcohol, or the neutral-relaxing SCQ, in which they described a situation resulting in a calm or peaceful state.

The SCQ asks the participant to describe a situation corresponding to a cue response (i.e., neutral-relaxing cue or alcohol cue) aloud to the researcher (i.e., "Describe the situation as though you are helping me see it as if I was there with you"). The SCQ includes the following prompt to elicit details from the participant: "Please include such details as who was there; what you were doing; where you were; how things looked; what bodily sensations you experienced." After the participant described the situation to the examiner, the examiner administered a list of various bodily sensations that may be experienced in different situations (e.g., heart beats faster, tension in back, feel like crying, etc.) and prompted the participant to circle all responses that he or she would normally experience in the situation he or she previously described, with an area to write down other sensations not listed. The researcher then verbally summarized the participant's answers on the SCQ, incorporating the bodily sensations into the summary. The participant was asked to close his or her eyes and prompted to continue imagining the neutral or alcohol-related situation for an additional 30 seconds. The cue exposure procedure is based on Miller and colleagues' (1987) work in personalized imagery training and Sinha and colleagues' (Sinha, Catapano, & O'Malley, 1999; Sinha et al, 2009) application of this imagery theory to cue exposure research. The SCQ is part of the Imagery Script Development Procedures Manual published by Sinha & Tuit (2012) to guide the use of imaginal cue exposure in substance use research.

Data Analytic Strategy

Working memory scores were measured by the proportion of the difference between total hits and total false alarms to the number of experimental blocks on the n-back task. Alcohol craving and subjective distress were each measured by a single-item

rating scale, ranging from 0-100. Alcohol craving was also measured by the ACQ-SF-R using the general craving index score. The single-item and ACQ-SF-R alcohol craving measures were also combined into an alcohol craving composite variable, which was used in the analyses.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured with a portable sphygmomanometer. Measurements were taken during 4 time periods (i.e., baseline, pre-cue working memory test, cue exposure, post-cue working memory test). Ten measurements were taken in 60-second increments during the baseline and cue exposure time periods and four measurements were taken in 60-second increments during both pre- and post-cue working memory tests, for a total of 28 blood pressure and heart rate measurements. The first, third, fifth, seventh, and ninth measurements of the ten measurements taken during the baseline and cue exposure time periods were averaged, and the four measurements taken during the pre- and post-cue exposure time periods were also averaged; the average scores for each time period were utilized in analysis of variance procedures. This procedure is consistent with past studies analyzing blood pressure and heart rate data (Chaplin, Hong, Bergquist, & Sinha, 2008; Ginty et al., 2014; Harden & Pihl, 1995; Panknin et al., 2002).

The data was analyzed utilizing 2-Group (alcohol, neutral) x 2-Time (pre, post) repeated measures analysis of variance (ANOVA) to examine the between-group and within-group differences in working memory, subjective distress, and alcohol craving scores. A 2-Group (alcohol, neutral) x 4-time (baseline, pre-cue exposure working memory, cue exposure, post-cue exposure working memory) repeated measures ANOVA was conducted to examine the between-group and within-group differences in heart rate,

systolic blood pressure, and diastolic blood pressure. Multiple regression was also utilized to predict post-cue working memory scores from post-cue alcohol craving and subjective distress scores, controlling for pre-cue levels of all variables, and to examine the interaction between post-cue exposure working memory scores and cue condition. Data was analyzed with IBM SPSS Statistics, Version 24 software.

CHAPTER THREE

Results

Sample Characteristics

The sample consisted of 91 participants, with 46 participants in the neutral-cue group and 45 participants in the alcohol-cue group. Blood pressure data (i.e., systolic and diastolic blood pressure and heart rate during 4 time periods: baseline; pre-cue working memory; cue exposure; and post-cue working memory) were collected for 68 participants, with 35 participants in the neutral-cue group and 33 participants in the alcohol-cue group. Participants were predominantly male (65.9%) and ranged in age from 21 to 58 years old (M = 39.03, SD = 9.71). The sample was composed of 82.4% Caucasian, 4.4% African American, 1.1% Asian, 1.1% Native American, and 3.3% Biracial participants, with 7.7% of participants identifying as, "Other." Additionally, 16.5% of the sample identified as Hispanic. Participants' length of time in treatment as of the day of study participation ranged from 3 to 88 days (M = 20.59, SD = 12.34) and 65.9% of the sample had been previously treated for a substance use disorder. Log-transformed data for subjective distress, alcohol craving, and working memory variables were used in the following analyses due to violation of the assumption of normality. Descriptive statistics for subjective distress, alcohol craving, and working memory raw scores, as well as raw scores for cardiovascular measures, are displayed in Tables 1 and 2, respectively.

Table 1

Means and Standard Deviations for Self-Report and Working Memory Measures

	Pre-Cue Exposure		Post-Cue Exposure	
Measures	Neutral	Alcohol	Neutral	Alcohol
Self-Report				
SUDS Rating	34.70 (25.55)	32.18 (25.48)	26.52 (23.45)	33.00 (24.51)
Craving Rating	17.61 (22.71)	20.78 (25.29)	10.67 (15.02)	24.44 (24.51)
ACQ-SF-R Score	3.38 (1.23)	3.29 (1.26)	3.19 (1.38)	3.27 (1.13)
ALC Composite	20.99 (23.37)	24.07 (26.20)	13.86 (15.78)	27.71 (25.36)
Working Memory				
Hits	25.63 (4.02)	25.38 (4.89)	27.04 (3.65)	26.00 (4.47)
False Alarms	1.28 (1.72)	1.71 (1.93)	1.26 (1.64)	1.47 (1.41)
Total Score	4.06 (.82)	3.94 (.96)	4.30 (.73)	4.09 (.82)

Note. Values indicate *M (SD)*. Neutral = neutral cue group; Alcohol = alcohol cue group; SUDS = Subjective Distress; Craving = Single-Item Alcohol Craving; ACQ-SF-R = Alcohol Craving Questionnaire- Short Form- Revised; ALC = Alcohol Craving; Total Score = ratio of difference between hits and false alarms to number of experimental blocks.

Table 2

Means and Standard Deviations for Cardiovascular Measures

	Baseline		Pre-Cue N-Back		Cue Exposure		Post-Cue N-Back	
Cardiovascular Measures	Neutral	Alcohol	Neutral	Alcohol	Neutral	Alcohol	Neutral	Alcohol
Heart Rate								
M	83.91	82.67	83.69	80.88	81.20	82.95	81.26	80.25
(SD)	(12.01)	(9.95)	(12.29)	(10.64)	(12.50)	(10.93)	(12.99)	(10.79)
Systolic Blood Pressure								
M	125.31	120.20	125.31	120.18	126.82	122.19	123.98	119.14
(SD)	(17.57)	(12.33)	(18.01)	(13.09)	(16.97)	(15.15)	(15.34)	(13.82)
Diastolic Blood Pressure								
M	71.98	72.50	72.87	72.17	73.34	73.72	71.62	70.75
(SD)	(13.13)	(8.49)	(13.23)	(8.53)	(12.89)	(9.85)	(12.35)	(10.07)

Note. Neutral = neutral cue group; Alcohol = alcohol cue group.

Baseline Between-Groups Comparisons

Independent samples t-tests were conducted to determine if participants in the alcohol- and neutral-cue groups differed significantly at baseline in subjective distress (SUDS rating), alcohol craving (single-item rating and ACQ-SF-R score), working memory (n-back) scores, systolic blood pressure, diastolic blood pressure, or heart rate. Results showed no significant differences between the alcohol- and neutral-cue groups for baseline scores on the SUDS rating ($t(89) = .24$, $p = .808$), single-item alcohol rating ($t(89) = -.53$, $p = .595$), ACQ-SF-R score ($t(89) = .37$, $p = .712$), n-back score ($t(89) = .75$, $p = .454$), or heart rate ($t(66) = .46$, $p = .648$). The Welch-Satterthwaite method was applied to the independent samples t-tests of baseline systolic and diastolic blood pressure due to the statistical significance of Levene's Test for Equality of Variances (SBP, $p = .028$; DBP, $p = .032$), and results showed no significant differences between the alcohol- and neutral-cue groups for baseline systolic ($t(61.08) = 1.39$, $p = .168$) or diastolic ($t(58.59) = -.19$, $p = .847$) blood pressure.

Test of the Effect of Cue Condition on Distress, Alcohol Craving, and Working Memory

A repeated-measures ANOVA revealed a statistically significant effect of time and condition on subjective distress, $F(1,89) = 4.72$, $p = .032$, partial $\eta^2 = .05$, and alcohol craving as measured by a single-item rating, $F(1,89) = 5.79$, $p = .018$, partial $\eta^2 = .06$, such that subjective distress and alcohol craving increased from pre- to post-test for the alcohol-cue group and decreased from pre- to post-test for the neutral-cue group. Pre- and post-cue scores for subjective distress and single-item alcohol craving are depicted in Figures 1 and 2, respectively. In contrast, the effects of time and condition on alcohol craving as measured by the ACQ-SF-R were not statistically significant, $F(1,89) = 1.88$, p

= .173, partial η^2 = .02 (see Figure 3). A craving composite variable was created by combining scores on the ACQ-SF-R and the single item alcohol craving measure, and this composite was used in subsequent analyses. A repeated-measures ANOVA revealed a statistically significant effect of time and condition on the craving composite, F(1,89) = 7.39, p = .008, partial η^2 = .08, such that the alcohol craving composite score increased from pre- to post-test for the alcohol-cue group and decreased for the neutral-cue group (see Figure 4).

There was a statistically significant effect of time on working memory performance, F(1,89) = 5.09, p = .026, partial η^2 = .05, such that both groups demonstrated significantly higher working memory scores at post-test. The effect of time and condition on working memory performance was not significant, F(1,89) = .08, p = .774, partial η^2 = .00. Pre- and post-cue working memory scores are depicted below in Figure 5.

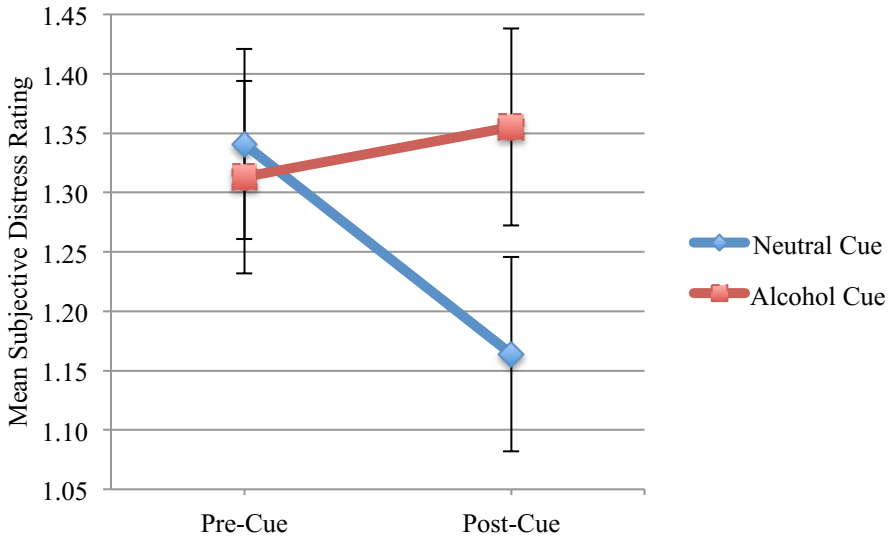


Figure 1. Subjective distress ratings from pre- to post-cue exposure. Time x condition interaction, p = .032. Error bars depict standard error estimates. Ratings were log-transformed.

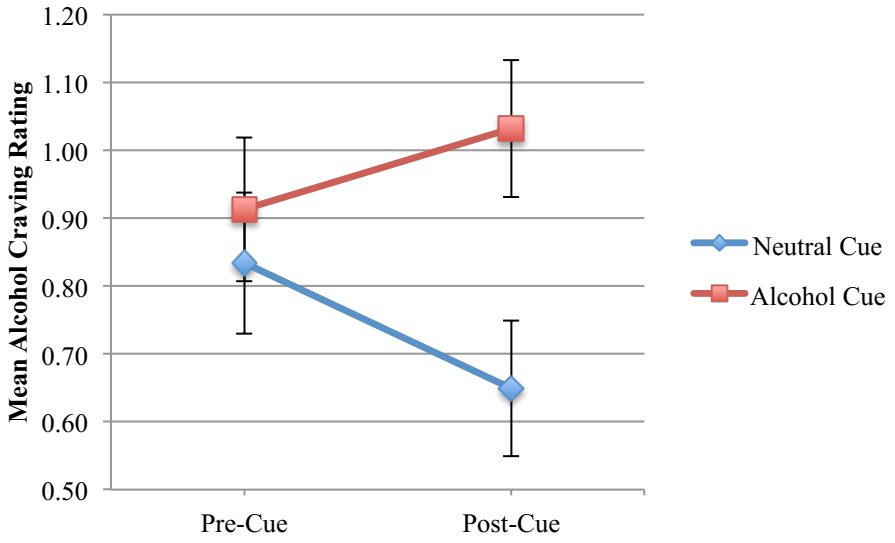


Figure 2. Alcohol craving ratings from pre- to post-cue exposure, single-item measure. Time x condition interaction, $p = .018$. Error bars depict standard error estimates. Ratings were log-transformed.

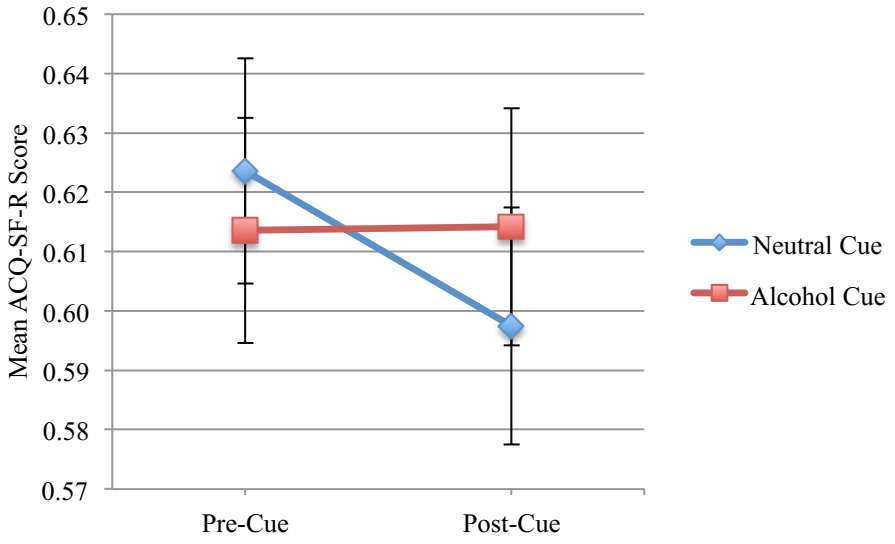


Figure 3. Alcohol Craving Questionnaire- Short Form- Revised (ACQ-SF-R) scores from pre- to post-cue exposure. No significant time x condition interaction. Error bars depict standard error estimates. General craving index scores were log-transformed.

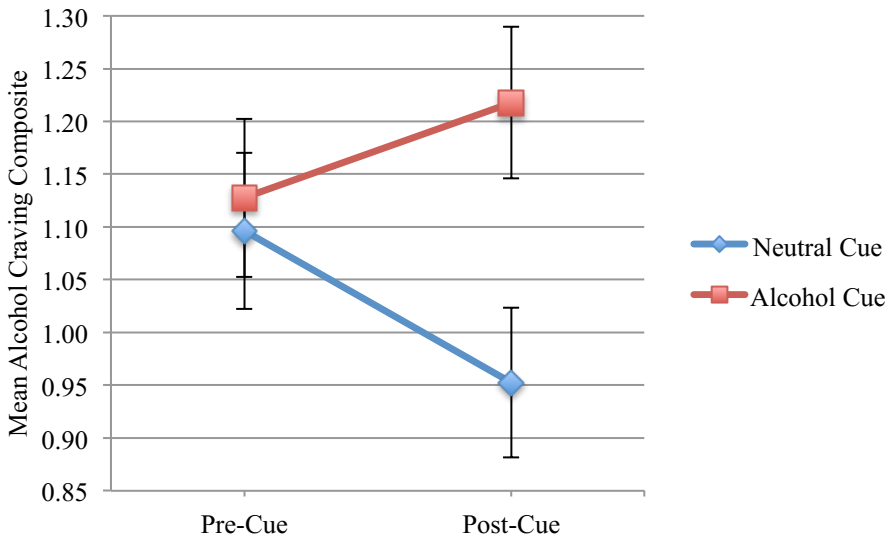


Figure 4. Alcohol craving composite scores from pre- to post-cue exposure. Time x condition interaction, $p = .008$. Error bars depict standard error estimates. Composite scores were log-transformed.

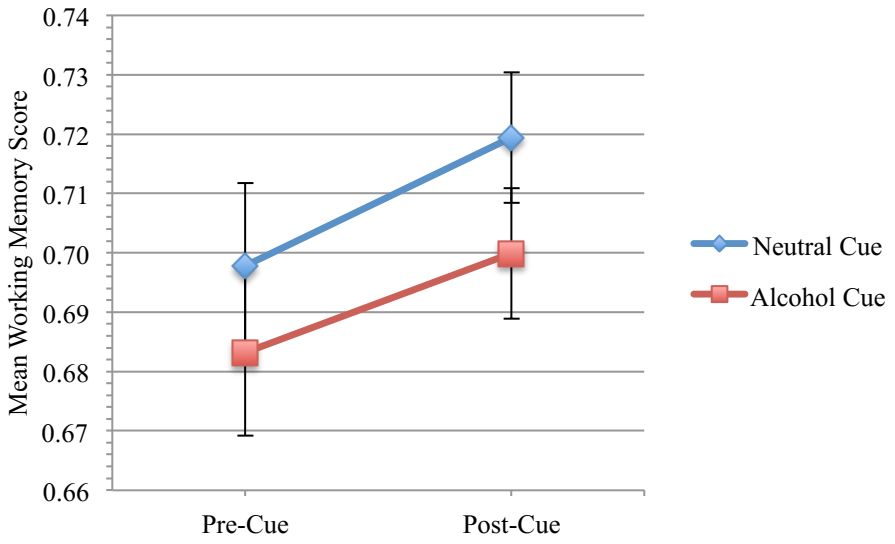


Figure 5. Working memory scores from pre- to post-cue exposure. Both cue groups: Pre-Cue < Post-Cue, $p = .026$. Error bars depict standard error estimates. Scores were log-transformed.

Test of the Effect of Cue Condition on Heart Rate and Blood Pressure

There was a statistically significant interaction between time and condition for heart rate, $F(2.46,162.32) = 5.77$, $p = .002$, partial $\eta^2 = .08$. The Greenhouse-Geisser

correction was applied to the results given the violation of the assumption of sphericity as indicated by the statistical significance of Mauchly's Test of Sphericity ($\chi^2(5) = 22.55$, $p < .001$). As shown in Figure 6, heart rate stayed relatively constant from baseline to cue exposure for the alcohol-cue group and decreased from baseline to cue exposure for the neutral-cue group. From working memory pre- to post-test, heart rate decreased dramatically in the neutral-cue group and decreased only slightly in the alcohol-cue group. Heart rate decreased significantly from cue exposure to working memory post-test in the alcohol-cue group, but it stayed relatively constant from cue-exposure to working memory post-test in the neutral-cue group.

There was a statistically significant effect of time on systolic blood pressure, $F(3,198) = 4.11$, $p = .007$, partial $\eta^2 = .06$, such that systolic blood pressure significantly declined in both groups from cue exposure to working memory post-test. The interaction between time and condition for systolic blood pressure was not significant, $F(3,198) = .04$, $p = .989$, partial $\eta^2 = .00$. As shown in Figure 7, systolic blood pressure showed a nearly identical pattern of fluctuation across the study protocol in both groups.

There was a statistically significant effect of time on diastolic blood pressure, $F(2.64, 174.32) = 3.63$, $p = .018$, partial $\eta^2 = .05$, such that diastolic blood pressure significantly declined in both groups from working memory pre- to post-test and from cue exposure to working memory post-test. The interaction between time and condition for diastolic blood pressure was not significant, $F(2.64,174.32) = .50$, $p = .658$, partial $\eta^2 = .01$. The Greenhouse-Geisser correction was applied to the results given the violation of the assumption of sphericity as indicated by the statistical significance of Mauchly's

Test of Sphericity ($\chi^2(5) = 15.68$, $p = .008$). As shown in Figure 8, diastolic blood pressure showed a similar pattern of fluctuation across the study protocol in both groups.

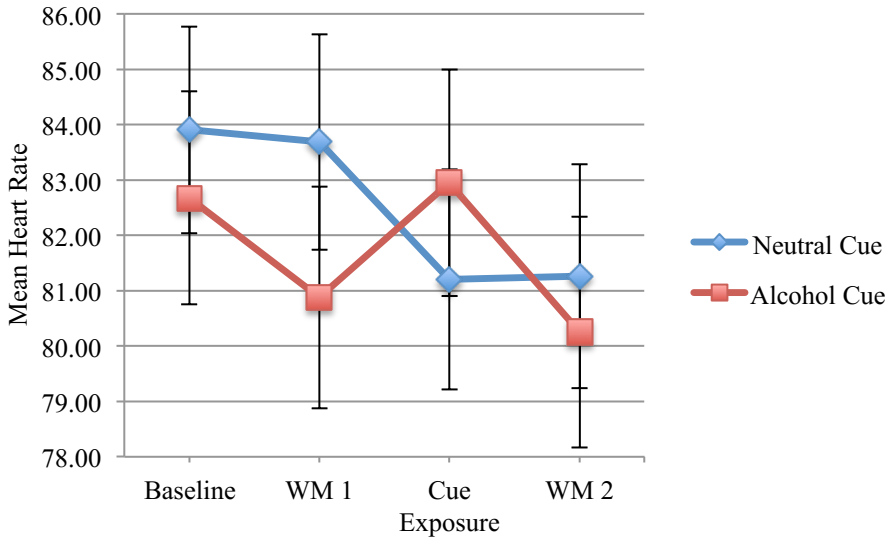


Figure 6. Heart rate measurements. WM = working memory. Neutral cue group: WM 1 > Cue Exposure, $p = .006$. Alcohol cue group: Baseline > WM 1, $p = .012$; WM 1 < Cue Exposure, $p = .026$; Cue Exposure > WM 2, $p = .006$. Error bars depict standard error estimates.

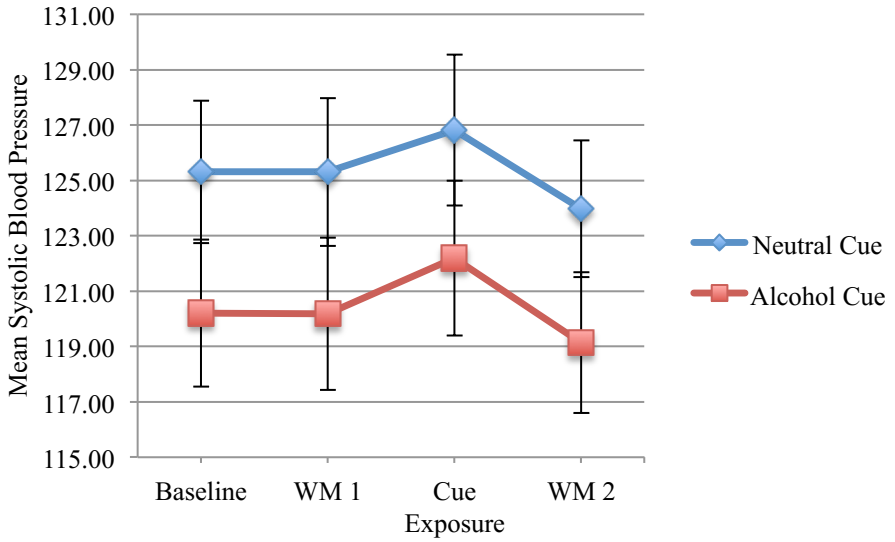


Figure 7. Systolic blood pressure measurements. WM = working memory. Neutral cue group: Cue Exposure > WM 2, $p = .010$. Alcohol cue group: Cue Exposure > WM 2, $p = .007$. Error bars depict standard error estimates.

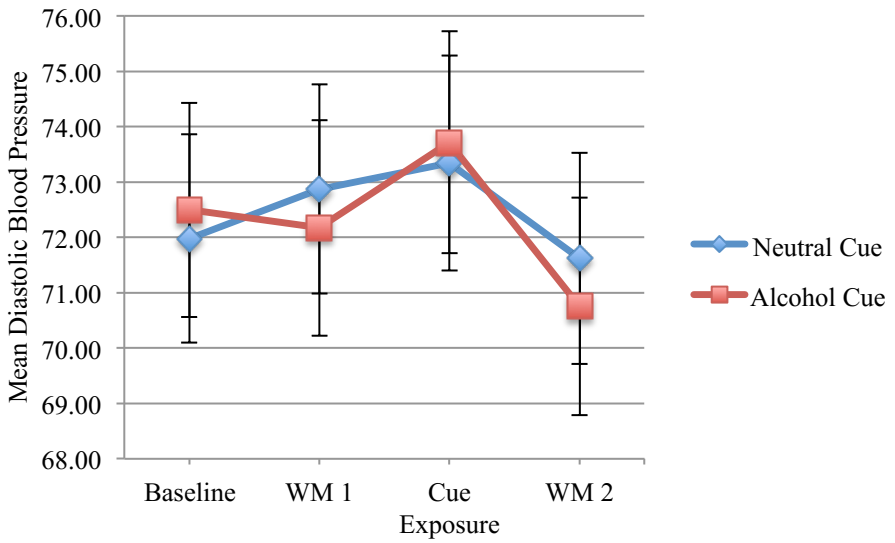


Figure 8. Diastolic blood pressure measurements. WM = working memory. Alcohol cue group: Cue Exposure > WM 2, $p = .011$. Error bars depict standard error estimates.

Predictors of Post-Cue Working Memory Scores

A multiple regression analysis was conducted to predict post-cue working memory score from cue condition (i.e., alcohol- versus neutral-cue group), pre-cue working memory score, and pre- and post-cue alcohol craving score. Pre-cue working memory score ($B = .43$, $p < .001$) significantly predicted post-cue working memory score ($F(4,86) = 10.80$, $p < .001$, $R^2 = .33$). Cue condition ($B = -.02$, $p = .184$), pre-cue alcohol craving ($B = .01$, $p = .595$), and post-cue alcohol craving ($B = .02$, $p = .309$) were not significantly predictive of post-cue working memory score. Due to significant correlation among subjective distress and alcohol craving scores, these measures were entered into separate regression models as predictors of post-cue working memory score. Pre-cue working memory scores, as well as cue condition, were included as predictors in each multiple regression analysis in accordance with Cohen & Cohen's (1983) method for multiple regression analysis in repeated-measures research designs. Cue condition ($B = -$

.01, p = .366), pre-cue subjective distress (B = -.00, p = .837), and post-cue subjective distress (B = -.01, p = .703) were not significant individual predictors of post-cue working memory score (pre-cue working memory, B = .42, p < .001; F(4,86) = 9.66, p <.001, R^2 = .31).

Relationships Among Variables

As shown in Table 3, the change from pre- to post-test in subjective distress was significantly correlated with the change in alcohol craving (r = .41, p < .001). There were no significant correlations between the change in working memory scores from pre- to post-test and the change in subjective distress or alcohol craving from pre- to post-test.

Table 3

Pearson Correlations Between Working Memory, Subjective Distress, and Alcohol Craving Change Scores

Change Scores	WM Change Score	SUDS Change Score	ALC Change Score
WM Change Score	-		
SUDS Change Score	.05	-	
ALC Change Score	-.10	.41**	-

Note. WM = Working Memory; SUDS = Subjective Distress; ALC = Alcohol Craving Composite.
**p < .001 level, two-tailed.

CHAPTER FOUR

Discussion

Summary of Findings

Results indicated that the personalized, imaginal alcohol cue exposure paradigm induced significant increases in subjective distress and alcohol craving as measured by a single-item rating scale. Conversely, participants in the neutral-cue group reported significant decreases in subjective distress and alcohol craving from pre- to post-cue exposure. These results suggest that the cue exposure procedure was successful in eliciting significant change in participants' subjective experience of distress and level of alcohol craving in the expected direction, with reductions in distress and craving in the neutral-cue group and increases in distress and craving in the alcohol-cue group. In contrast, changes in scores on the 12-item Alcohol Craving Questionnaire, Short Form, Revised (ACQ-SF-R) from pre- to post-cue exposure were not statistically significant, suggesting that change in alcohol craving was not captured by this longer measure.

Additionally, results demonstrated that working memory scores significantly increased from pre- to post-cue exposure in both groups, with no statistically significant difference in degree of improvement between groups. By extension, no significant correlation was found between change in working memory score from pre- to post-cue exposure and change in subjective distress or alcohol craving from pre- to post-cue exposure. These findings suggest that working memory performance was not significantly affected by alcohol cue exposure.

Regarding cardiovascular responses throughout the study protocol, significant between-group differences were found for heart rate measurements. In the alcohol-cue group, heart rate stayed relatively constant from baseline to cue exposure, decreased only slightly from working memory pre- to post-test, and decreased dramatically from cue exposure to working memory post-test; conversely, in the neutral-cue group, heart rate decreased from baseline to cue exposure, decreased from working memory pre- to post-test, and stayed relatively constant from cue exposure to working memory post-test. However, despite these differences in heart rate across the study protocol, results indicated that heart rate was not significantly increased by alcohol cue exposure; in fact, heart rate stayed relatively constant from baseline to cue exposure in the alcohol-cue group. In addition, systolic and diastolic blood pressure were not significantly different between groups at any point in the study protocol, and those measures did not demonstrate statistically significant change during alcohol cue exposure.

Working Memory Performance

The hypothesis that participants in the alcohol-cue group will demonstrate attenuated improvement in working memory following the cue exposure as compared to the neutral-cue group was not supported, as both groups demonstrated improved performance with no significant difference in the degree of improvement between groups. Thus, the related hypothesis that the difference between pre- and post-cue working memory scores will be negatively correlated with the differences between pre- and post-cue subjective distress and alcohol craving scores in the alcohol- and neutral-cue conditions was not supported. The improvement in working memory performance across both groups, paired with significant group differences in report of subjective distress and

alcohol craving from pre- to post-cue exposure, made the hypothesized correlations impossible.

Regarding working memory performance, practice effects for n-back working memory tasks have been documented in the literature and the results of the current study are in accordance with research demonstrating improved n-back task performance with repetition (Buschkuehl, Hernandez-Garcia, Jaeggi, Bernard, & Jonides, 2014; Collie, Maruff, Darby & McStephen, 2003; McEvoy, Smith, & Gevins, 1998; Murray, McFarland, & Geffen, 2005; Price, Colflesh, Cerella, & Verhaeghen, 2014; Soveri et al., 2018). The current findings suggest that the practice effect for n-back performance overcame any detrimental effect on performance arising from increased alcohol craving following imaginal alcohol cue exposure.

More specifically, the practice effect in the current study may have been enhanced by the inclusion of multiple practice trials for the working memory task. Participants completed a practice trial for each level of the n-back task prior to the pre-cue exposure working memory task in order to ensure adequate learning of the task. The same task was utilized for the post-cue working memory measurement, including the practice trials, giving participants an additional opportunity to bolster their performance on the task. This flaw in the research design may have inadvertently enhanced practice effects and minimized the likelihood that working memory performance would be impacted by the alcohol cue exposure.

Similarly, the use of the same task for pre- and post-cue working memory measurement may have contributed to practice effects overwhelming the effects of the alcohol cue exposure. While previous studies examining working memory performance

have utilized the same task in a repeated-measures study design (Brunyé, Moran, Holmes, Mahoney, & Taylor, 2017; Cevik & Alton, 2016; Lindheimer, O'Connor, McCully, & Dishman, 2017), the hypothesis in the current study may have been better served by utilizing an alternate version of the n-back task, such as two n-back tasks using different stimuli (e.g., one task with letter stimuli and one task with number or image stimuli). Reduced practice effects have been found when using alternate forms in repeated assessment with a variety of neuropsychological tests, including verbal and nonverbal memory tests (Benedict, 2005; Benedict & Zgaljardic, 1998; Pereira, Costa, & Cerqueira, 2015). While Beglinger et al. (2005) found that alternate versions of working memory tasks only minimally reduce practice effects and novel tasks show reduced benefit from the use of alternate forms, the study involved repetitious working memory trials over multiple sessions, a vastly different research design from that of the current study. Use of an alternate form during one session after a single experimental manipulation, as in the research design for the current study, may have resulted in adequate reduction of practice effects while maintaining the integrity of the construct being assessed.

Cue Exposure Procedure

In further explanation of the working memory findings, it is also possible that the alcohol cue exposure lacked the potency to induce a craving state sufficiently strong enough to disrupt cognitive performance. The cue exposure procedure utilized in the current study was modeled after the procedure used in studies by Fox et al. (2007) and Sinha et al. (2009) and developed by Sinha & Tuit (2012) to apply imaginal cue exposure techniques in research with individuals with AUD; however, the procedures in the current

study differed from those developed by Sinha & Tuit (2012) in some ways that may have resulted in reduced potency of the imagery scripts. The procedures developed by Sinha & Tuit (2012) include a laboratory session prior to the cue exposure in which a researcher develops a number of vivid imagery scripts with the participant, and the most craving-inducing script is chosen for use in the cue exposure session. Additionally, the researcher creates an audio recording of the imagery script to be used during the cue exposure, and the cue exposure session consists of the participant listening to the recording with headphones. A different researcher unfamiliar with the participant's script then administers the post-cue exposure measures.

In order to reduce the burden of participation, the procedures in the current study did not include an initial laboratory session solely for script development; instead, participation included a single laboratory session in which the cue exposure was created utilizing Sinha & Tuit's (2012) procedures, and the researcher administered the cue exposure to the participant aloud immediately following script development. The lack of development of multiple imagery scripts, and thus the lack of ability to choose the script resulting in the strongest intensity of craving, reduced the potential for optimal potency in eliciting alcohol craving.

Additionally, the difference in modality of cue exposure administration (i.e., verbal, researcher administration versus audio recording) may have affected the strength of craving experienced by participants. It is possible that an increased sense of privacy when listening to an audio-recorded script, as in Sinha & Tuit's (2012) procedures, may allow participants a heightened ability to fully engage in vivid imagination given the absence of interaction with a researcher during the script. In contrast, the inherent social

nature of the researcher-administered script in the current study may have inadvertently reduced the ability of participants to engage in the imaginal exercise. Individuals with AUD may cognitively avoid attending to alcohol cues due to the aversive nature of the experience, and lack of attention to the cue may reduce cue reactivity (Niaura et al., 1988). Participants may be more apt to engage in cognitive distraction during a cue exposure administered by a researcher, such as focusing on thoughts about the researcher's potential reactions or perceived judgments, as compared to a cue exposure administered via audio recording, in which concerns about social evaluation are eliminated and attentional distraction is reduced. It is also possible that the setting of the study inside treatment facilities contributed to attenuated cravings, as presence in a treatment facility may have primed participants to deny cravings or to experience craving less intensely due to perceptions of the treatment environment as safe and supportive.

In contrast to the alcohol cue group, participants in the neutral cue group demonstrated significant reduction of alcohol craving, subjective distress, and heart rate from baseline to cue exposure, indicating that the neutral/relaxing cue exposure successfully induced a relaxed state. Additionally, the neutral cue group showed an increase in working memory scores from pre- to post-cue exposure. These results are aligned with the implication in the study hypotheses that the neutral cue group would experience a reduction in arousal coupled with improved working memory performance.

These findings suggest that the imaginal cue exposure procedure utilized in the current study was sufficient to induce a neutral/relaxed state in participants. It is possible that, as previously discussed, the imaginal cue exposure procedure was effective in eliciting changes in distress and craving in both groups, but those changes did not affect

working memory performance due to practice effects. Conversely, it is possible that participants in the neutral cue group were more able or willing to engage fully in the imaginal exercise as compared to those in the alcohol cue group, and thereby experienced the expected reductions in distress and craving as a result of the cue exposure. While the cue exposure procedure for the neutral/relaxing cue group was identical to the alcohol cue group and thus faced the same possible confounding variables (e.g., administration affected by social interaction, lack of prior laboratory session for imagery script development), engaging in a neutral/relaxing imagery paradigm is likely to be considerably less threatening and stressful for an individual with AUD as compared to an alcohol imagery paradigm. Participants in the neutral/relaxing cue group may have engaged in less cognitive avoidance of the cue exposure content than those in the alcohol cue group, and thereby evidenced subjective and physiological effects consistent with the neutral/relaxing cue.

Measurement of Alcohol Craving

In addition to the possible effects of changes to the cue exposure procedure, discrepancy between alcohol craving measures may suggest that the alcohol cue exposure did not elicit the strength of craving required to impact working memory performance. While the single-item measure of alcohol craving evidenced significant changes in both groups as a result of the cue exposure in the expected directions, the more comprehensive, 12-item measure of alcohol craving did not show commensurate change from pre- to post-cue exposure. Single-item measures of alcohol craving have been used widely in alcohol use research (Coffey, Stasiewicz, Hughes, & Brimo, 2006; Khemiri et al., 2015; Koopmann et al., 2017; Leggio et al., 2014; Li et al., 2015; Mathis & Han,

2017; Sayette et al., 2000; Tiffany et al., 2000; Wedekind et al., 2010); in fact, two studies with very similar procedures to the current study (i.e. repeated-measures design examining response to imaginal alcohol cue exposure) utilized single-item, visual analog scales to measure distress and alcohol craving (Fox et al., 2007; Sinha et al., 2009). However, the discrepancy between the ACQ-SF-R and the single-item measure of alcohol craving in the current study is cause for further examination of the measurement of acute alcohol craving.

Single-item measures of alcohol craving are often favored in research given their acceptability and feasibility for use in studies examining acute alcohol craving in response to an experimental manipulation (Sayette et al., 2000). Single-item measurement of alcohol craving has the unique benefit of allowing research participants the ability to rate their level of craving quickly and immediately following an experimental manipulation, as compared to a longer questionnaire that may allow for reduction in craving due to the passage of time or active coping (Sayette et al., 2000). For this reason, single-item measurement of alcohol craving may result in the most accurate assessment of craving in response to alcohol cue exposure.

Additionally, results of a study comparing a single-item and multi-item measure of alcohol craving demonstrated that the single-item measure evidenced superior criterion validity as compared to the 10-item measure (Connor, Feeney, & Young, 2005). A study by Li et al. (2015) examining changes in level of cue reactivity across time in a group of individuals with AUD found that a single-item, visual analog scale measuring subjective craving was more sensitive to changes in alcohol craving than the Alcohol Urge Questionnaire, an 8-item measure of alcohol craving. Further, studies demonstrating

significant increases in self-reported alcohol craving on a single-item measure following an alcohol cue exposure have also shown evidence of corresponding physiological increases in arousal (Carter & Tiffany, 1999; Cooney et al., 1997; Kaplan et al., 1985; Sinha et al., 2009; Staiger & White, 1991). These results offer evidence for the criterion and construct validity of single-item alcohol craving measures.

A possible explanation for the discrepancy between self-report craving measures is measurement of different constructs. Connor et al. (2005) failed to find a significant association between the Borg Craving Scale, a single-item visual-analog craving rating scale, and the Yale-Brown Obsessive Compulsive Scale- heavy drinking, a 10-item measure of alcohol craving, in a study with alcohol-dependent individuals in outpatient treatment. The lack of correlation between single-item and multi-item measures found in the current study is consistent with the findings of Connor et al. (2005), and may suggest that the questionnaires are not measuring the same construct. The four subscales of the ACQ-SF-R measure a variety of aspects of the overall construct of craving, and may therefore lack correlation with a single-item rating.

Given the findings of the current study, the reason or combination of reasons for improvement in working memory scores in both groups coupled with disagreement in subjective report of alcohol craving across two self-report measures is unknown. It is possible that practice effects overcame the effect of increased alcohol craving. Conversely, the alcohol cue exposure may have effectively increased alcohol craving, but the craving was not strong and/or enduring enough to be captured by the ACQ-SF-R. It is also possible that the single-item scale and the ACQ-SF-R measure inherently different constructs.

Cardiovascular Response to Cue Exposure

The hypothesis that systolic blood pressure and heart rate will increase for the alcohol-cue group during the cue exposure was not supported; heart rate declined from baseline to pre-cue working memory in the alcohol-cue group, and returned to approximate baseline level during the cue exposure. Further, systolic blood pressure did not differ significantly between the alcohol- and neutral-cue groups at any time point. Similarly to the discussion of working memory performance, it is possible that the potency of the imaginal cue exposure paradigm was insufficient to induce physiological arousal in participants in the alcohol cue group. Notably, these cardiovascular findings are contrary to those of Sinha et al. (2009) in which heart rate and systolic blood pressure were significantly elevated during an imaginal alcohol cue exposure as compared to baseline heart rate and blood pressure in a group of alcohol-dependent individuals; however, the findings of the current study support those of Fox et al. (2007) in which individuals with AUD reported significant alcohol craving during an imaginal alcohol cue exposure, but did not show commensurate change in blood pressure or heart rate.

One possible explanation for lack of heart rate and blood pressure increase in response to alcohol cues in the current study is the experience of transient withdrawal hypertension, which is common in individuals with AUD who are recently abstinent, particularly in the first 4 weeks of abstinence (Ceccanti et al., 2006; King, Parsons, Bernardy, & Lovallo, 1994). Research linking hypertension with decreased heart rate variability (Schroeder et al., 2003) suggests that individuals experiencing hypertension may not evidence an increase in heart rate or blood pressure in response to cues. Participants' length of stay in treatment at the time of study participation, and therefore

length of sobriety from alcohol, may offer a partial explanation for the divergence of the current findings from those of Sinha et al. (2009) given the possibility of transient withdrawal hypertension. While the participants in Sinha et al. (2009) had been in treatment for at least 28 days at the time of participation and thereby were less likely to be experiencing withdrawal-related hypertension, the current study included participants who ranged widely from 3 to 88 days in treatment at time of participation and may thus have included participants experiencing hypertension as a result of post-acute alcohol withdrawal. The current study included participants from two treatment facilities, one of which consisted of a 30-day treatment program; in order to maximize potential study eligibility, data collection was not limited to participants with 28 days or more of sobriety, which increased the likelihood of including participants experiencing transient withdrawal hypertension.

Similarly to the current study, Reid et al. (2006) found no increase in heart rate for individuals with AUD in response to an alcohol cue exposure; however, Reid et al. (2006) found a significant increase in skin conductance during the alcohol cue exposure, reflective of autonomic arousal in response to alcohol cues not captured by cardiovascular measures. Further, despite no evidence of blood pressure reactivity, Fox et al. (2007) found significant increases in salivary cortisol during the alcohol cue exposure suggestive of cue-induced hypothalamic-pituitary-adrenal (HPA) axis response. Given this precedent for the presence of physiological cue reactivity in the form of increased skin conductance and salivary cortisol levels despite a lack of change in heart rate or blood pressure, it is possible that physiological cue reactivity was not captured in the current study due to the exclusion of additional physiological measures.

In contrast, another possible explanation for the heart rate and blood pressure findings in the current study is related to dysregulation of the stress response in individuals with AUD. In a study by Panknin et al. (2002), individuals showed an attenuated cardiovascular response to a stress task as compared to healthy controls, which is aligned with reviews by Milivojevic, Fox, & Sinha (2015) and Blaine & Sinha (2017) documenting reduced HPA-axis and autonomic responses to stress and alcohol cues in individuals with AUD. These findings are aligned with some of those in the current study, in which participants in the alcohol-cue group demonstrated diminished heart rate response to the working memory tasks, such that lower heart rate was observed during the working memory tasks as compared to baseline heart rate. N-back tasks have been used as stress induction paradigms in previous research (Aranovich, McClure, Fryer, & Mathalon, 2016; Hu, Lamers, de Geus, & Penninx, 2016; Hu, Lamers, Hiles, Penninx, & de Geus, 2016; van Well, Kolk & Klugkist, 2008), and thus the findings of reduced heart rate during the working memory task are in contrast with the normative response of increased heart rate and are aligned with the attenuated stress response observed by Panknin et al. (2002). Additionally, participants in the current study, as in the study completed by Panknin et al. (2002), reported a subjective increase in distress and alcohol craving as a result of the alcohol cue exposure despite attenuated cardiovascular response. Dysfunction in the HPA axis and autonomic stress responses may explain the failure to show normative cardiovascular response in alignment with the stressful states elicited during the study protocol.

Limitations and Directions for Future Research

The results of the current study are limited by various aspects of the research design. Use of the same working memory task for both pre- and post-cue exposure measurements likely resulted in substantial practice effects. Future studies may consider utilizing an alternate form in order to minimize the influence of practice effects. Additionally, the divergence from the imaginal cue exposure procedures of Sinha & Tuit (2012) may have reduced the potency of the alcohol cue exposure, such that future studies may benefit from following the procedures with fidelity to ensure adequate levels of cue reactivity. The heterogeneity of participants' length of time in treatment at the time of study participation may have also affected cue reactivity and cardiovascular response to cue exposure in the current sample; by extension, less variability in days in treatment may allow for more robust findings in future studies. Further, utilizing only cardiovascular measures of physiological cue reactivity limited the findings of the current study. Given the disagreement in the literature regarding the physiological cue reactivity of individuals in treatment for AUD, future studies might include additional physiological measures, such as skin conductance and salivary cortisol, in order to elucidate the relationship between subjective and objective cue reactivity.

It is important to note that the current study examined working memory performance based on the relevance of working memory processes in making decisions about behavior during stressful situations, such as the decision that an individual with AUD must make when faced with alcohol cues in the community following residential treatment. However, working memory ability is only one of myriad factors that may contribute to such a decision-making process. For instance, level of motivation to

maintain sobriety, cognitive distortions regarding a personal ability to control amount of alcohol intake, and contextual factors such as the presence or absence of other individuals who are drinking or negative mood states are likely to affect relapse and are not captured in the measurement of working memory performance. Thus, the current study lacks a degree of ecological validity regarding the assessment of an individual's true ability to maintain sobriety in situations that pose high risk for alcohol relapse. Future studies might consider using more ecologically valid assessment tools, such as the Iowa Gambling Task (Bechara, 2007) to assess decision-making ability or the Alcohol-Specific Role Play Test (Monti et al., 1993) to assess ability to respond to vignettes involving high relapse risk situations. Given that these tests are also vulnerable to practice effects, researchers would benefit from carefully considering study methodology to bolster the likelihood of reaching valid conclusions.

Ultimately, the methodological issues in this study diminish the ability to draw strong conclusions about the effects of subjective and physiological cue reactivity on working memory performance for individuals with alcohol use disorder in residential treatment. With the aforementioned changes to the study design, it is possible that future studies may offer insight into the relationship between cue reactivity and working memory, and thereby add vital information to the understanding of the neuropsychological processes involved in alcohol relapse.

APPENDICES

APPENDIX A

Measures

Demographic & Inclusion/Exclusion Criteria Questionnaire

Gender: _____ Male _____ Female

Age: _____

Race: _____ Caucasian _____ African American _____ Asian _____ Latino/a

_____ Native American _____ Alaska Native _____Biracial _____ Other

Ethnicity: _____ Hispanic _____ Non-Hispanic

Length of Time in Treatment as of Today: _____ months, _____ days

Have you ever been diagnosed with a substance use disorder (Alcohol Use Disorder, Cannabis Use Disorder, etc.)?

_____ Yes _____ No

If yes, please list any substance use disorder diagnoses here:

_____
_____
_____
_____
_____

Have you ever been treated for a substance use disorder in the past? _____Yes_____ No

If yes, please list the substances for which you have been treated:

_____
_____
_____
_____
_____
_____

If yes, please list the number of times that you have engaged in:

Long-term inpatient treatment (more than 60 days): _____

Short-term inpatient treatment (up to 60 days): _____
Intensive outpatient treatment (9-12 hrs per week): _____
Outpatient treatment (less than 9 hrs per week): _____

Have you ever been diagnosed with a mood disorder (Major Depressive Disorder, Bipolar II Disorder, etc.)?

_____ Yes _____ No

If yes, please list any mood disorder diagnoses here:

_____
_____
_____
_____
_____

Have you ever been diagnosed with a psychotic disorder (Schizophrenia, Brief Psychotic Disorder, etc.)?

_____ Yes _____ No

If yes, please list any psychotic disorder diagnoses here:

_____
_____
_____
_____
_____

Have you consumed alcohol in the past 7 days?

_____ Yes _____ No

Have you ever experienced a craving (i.e., strong desire) for alcohol?

_____ Yes _____ No

Are you currently experiencing symptoms of withdrawal from substances (shakiness or trembling, nausea or vomiting, sweating, irritability, fatigue, headaches, etc.)?

_____ Yes _____ No

Are you currently taking any psychotropic (e.g., antidepressants, stimulant medication, etc.) or analgesic (e.g., pain-relieving medications) prescription medications?

_____ Yes _____ No

If yes, please list all prescribed psychotropic and analgesic medications:

_____
_____
_____
_____
_____

Were any of these medications started in the last month?

_____ Yes _____ No

Were any of these medication doses adjusted in the last month?

_____ Yes _____ No

Subjective Units of Distress Scale (SUDS): The Distress Thermometer

Rate your anxiety or discomfort on a scale from 0-100. Imagine you have a 'distress thermometer' to measure your feelings according to the scale below.

100- Extreme anxiety or discomfort

75- High anxiety or discomfort

50- Moderate anxiety or discomfort

25- Slight anxiety or discomfort

0- No anxiety or discomfort at all

Alcohol Craving Rating Scale: The Craving Thermometer

Rate your craving for an alcoholic drink on a scale from 0-100. Imagine you have a 'craving thermometer' to measure your feelings according to the scale below.

100- Extreme craving

75- High craving

50- Moderate craving

25- Slight craving

0- No craving at all

Scene Construction Questionnaire (Neutral-Relaxing)

We would like you to describe a situation you found most neutral-relaxing. Relaxing situations are those that put you in a calm and peaceful state and not one that is happy, joyous, exciting or stimulating in any way. Choose a situation that involves you alone and not someone else. Also, include in your description the bodily sensations you would experience if you were in the situation.

Sometimes it is difficult to think of a neutral, relaxing situation "on the spot". It may help to close your eyes and try to imagine yourself in the situation. While you are imagining the situation, try to generate the same sensations and feelings you would experience if you were actually in the situation. Describe the situation as though you are helping me see it as if I was there with you. (Please include such details as who was there; what you were doing; where you were; how things looked; what bodily sensations you experienced.)

Scene Construction Questionnaire (Alcoholic Drink)

We would like you to describe a situation when you wanted to have an alcoholic drink and you went ahead and had one. These would be situations that include explicit alcohol-related triggers that later led to drinking (e.g. buying alcohol, being at a bar, watching others drink alcohol). Also, include in your description the bodily sensations you would experience if you were in the situation.

Sometimes it is difficult to think of a situation "on the spot". It may help to close your eyes and try to imagine yourself in the situation. While you are imagining the situation, try to generate the same sensations and feelings you would experience if you were actually in the situation. Describe the situation as though you are helping me see it as if I was there with you. (Please include such details as who was there; what you were doing; where you were; how things looked; what bodily sensations you experienced prior to actual drink.)

Listed below are a number of bodily sensations that people normally experience in various situations. Circle all of the responses that you would normally experience in the above situation. Add any others that you may have experienced in the above situation.

Heart stops
Heart beats slower
Heart beats faster
Heart pounds
Heart skips a beat
Sweat pours out
Tightness in the face
Cramps in the stomach
Breathes faster
Breathes slower
Gasping for air
Feel tense all over
Heart quickens
Feel sweaty
Grit my teeth
Heart races
Stomach is in a knot
Pants/gasping for breath
Butterflies in the stomach
Shallow breathing

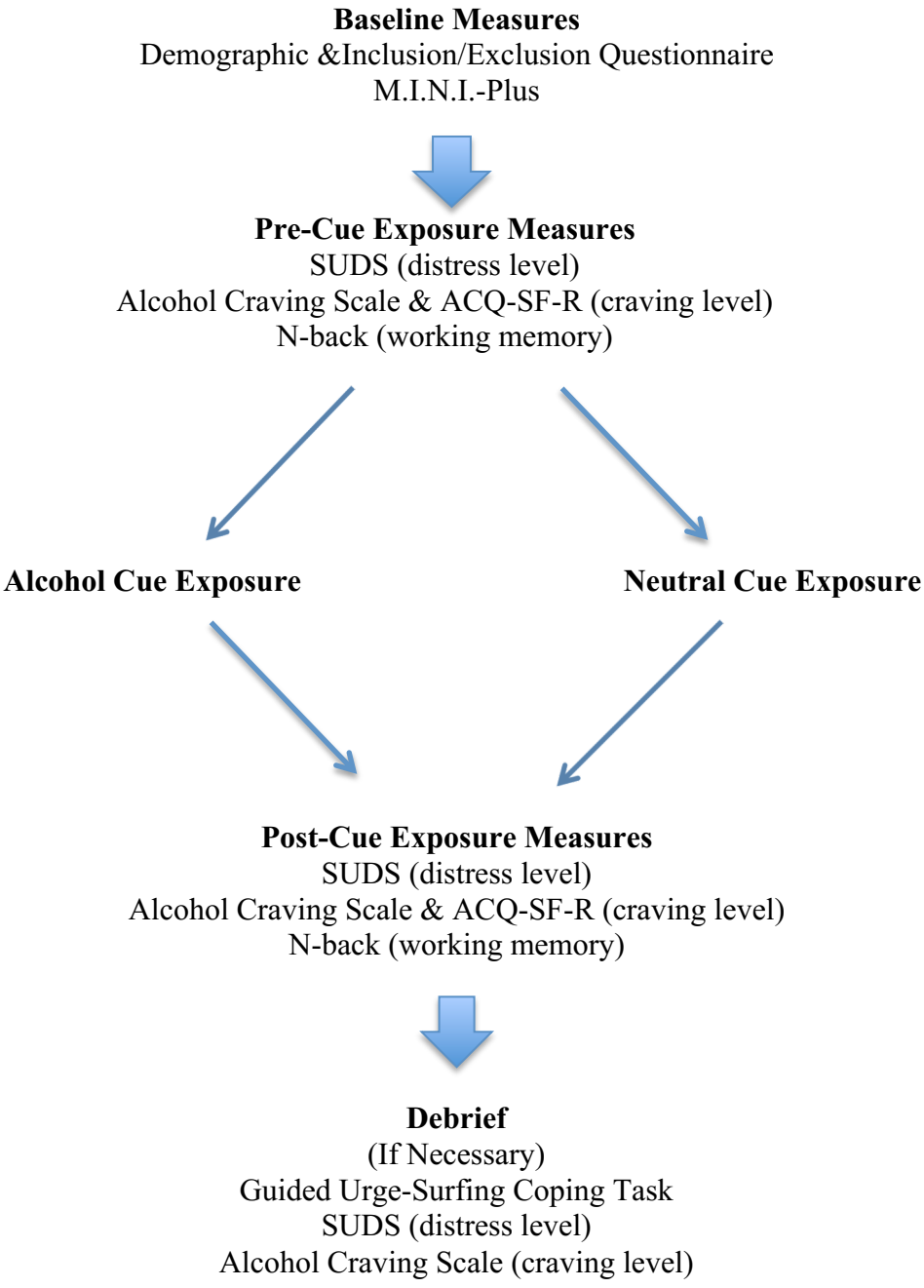
Labored breathing
Tension in the forehead
Clenched fist
Beads of perspiration
Tension in back
Tension in the arms
Whole body shakes
Feel hot all over
Flushed face
Feel warm
Jittery
Want to smash something
Palms are clammy
Clenched jaw
Hands trembling
Eyes water
Feelings seem dulled
Feel like singing
Physically less responsive
Feel strong inside
General sense of release
Sense of lightness, buoyancy and upsurge of the body
A sharpening of senses
Inner warm, glowing radiant sensation
Feeling choked up
Sinking feeling in my chest
Nauseous
Eyes burn
Constriction in the chest
Head pounds
Feel restless
Want to scream or strike someone
Sweat oozes out
Eye twitches
Blood rushes to my head
Lump in my throat
Lessening of tension
Heavy feeling in my stomach
Warm excitement
Feel like crying
Sense of being more alive
Want to hold time; capture the moment
Feel like smiling or laughing; heaviness in the chest
Feeling empty, drained, hollow
Deep intense pain sensation
Hurts to be alive
Tears come to my eyes

OTHER SENSATIONS:

Sinha, R. & Tuit, K. L. (2012). *Imagery Script Development Procedures*. New Haven, CT: Yale University School of Medicine.

APPENDIX B

Diagram of Study Procedure



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