Assessing Momentary Levels of Craving and Anxiety before and after Virtual Reality Cue-Exposure Therapy in individuals with Alcohol Use Disorder

Lena Franke

UNIVERSITY OF TWENTE

Faculty of Behavioural, Management, and Social Sciences

Department of Psychology, Health & Technology

Master thesis Positive Clinical Psychology and Technology

1st Dr. Alexandra Ghiţă and 2nd Dr. Christina Bode

August 18, 2021

Abstract

Background: Alcohol craving and craving-related anxiety are considered essential mechanisms that interfere with successful abstinence in individuals suffering from alcohol-use disorder (AUD). Cue-exposure therapy (CET) aims at reducing alcohol craving and craving-related anxiety. Virtual reality (VR) might increase the effectiveness of traditional CET. The current study investigated the extent to which ALCO-VR, a VR software, can be used to induce and assess craving/anxiety during exposure to alcohol-related VR-environments. Second, it was examined to what extent ALCO-VR can be used as a virtual-reality CET (VR-CET) tool to reduce momentary levels of craving/anxiety from pre- to post-treatment. *Methods:* A within-subject, repeated-measures design was applied. 19 participants from the Addictive Behaviour Unit of the Hospital Clinic of Barcelona took part. The study lasted five weeks for each participant and consisted of an initial assessment, six VR-CET sessions, and a final assessment. Momentary levels of craving and anxiety were assessed with visual analog scales (VASs). For the first aim, the levels of craving/anxiety in a neutral, non-alcohol-related environment were compared to the levels of craving/anxiety in four alcohol-related environments (bar, restaurant, at-home, pub). For the second aim, the levels of craving/anxiety at the initial and final assessment were compared. *Results:* Apart from anxiety in the at-home environment, the levels of craving/anxiety were significantly higher in the alcohol-related environments compared to the neutral environment. The momentary levels of craving/anxiety significantly decreased from pre- to post-VR-CET in all alcohol-related environments. *Discussion:* The findings support the effectiveness of the ALCO-VR software as an assessment and treatment tool for alcohol craving and craving-related anxiety. Larger clinical trials are required to investigate individual differences regarding VR-CET outcomes and to examine its long-term effects and ecological validity. Follow-ups to the current study are already ongoing to examine the long-term effects of VR-CET and its effectiveness in reducing relapse.

Keywords: Cue-exposure therapy, alcohol use disorder, alcohol-craving, craving-related anxiety, Virtual reality

Table of content

Introduction

The treatment of alcohol use disorder (AUD) is a holistic process consisting of psychosocial, behavioral, and pharmacological interventions. Still, relapse is a common problem for individuals with AUD and poses a threat to the effectiveness of treatment and, thus, to the well-being and quality of life of those affected [Campbell et al., 2018; Degenhardt et al., 2017; National Institute of Drug Abuse (NIDA), 2012]. Despite the existence of evidence-based guidelines on the treatment of AUD and advances in AUD treatment, there has been a rise in the prevalence of AUD, and relapse continues to be a significant problem [Campbell et al., 2018; NIDA, 2012; World Health Organization (WHO), 2019].

Underlying mechanisms in alcohol use disorder

One of the mechanisms that interfere with abstinence maintenance after treatment is craving, which is an uncontrollable and strong urge to consume a substance that can result in physical and psychological suffering when the "pathological appetite" for alcohol is not satisfied (Addolorato et al., 2001; Drummond, 2001; Pareaud et al., 2021; Stohs et al., 2019). Craving is one of the eleven criteria for a diagnosis of AUD in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5; American Psychiatric Association, APA, 2013) and is related to the severity of dependence as well as to the development of alcohol drinking patterns and maintenance of abstinence (Addolorato et al., 2001; APA, 2013; Berridge & Robinson, 2016; Kwon et al., 2006; Wapp et al., 2015; Zironi et al., 2006). During abstinence from alcohol, craving can be elicited by an alcoholic beverage but also and especially by the whole context of alcohol consumption and the stimuli present at that time. This situational reliance or context-dependency is based on associative learning, a process part of the classical conditioning theory by Pavlov (1927). Specifically, cues and contexts that have been repeatedly paired with the addictive substance during consumption become conditioned stimuli (CS) and can elicit craving independently of the substance itself. This means that craving can be elicited by the alcoholic cues and contexts that previously became associated with alcohol drinking and its reinforcing effects. The process of craving elicitation by alcohol cues and associated contexts is called cue-reactivity. The cue-reactivity paradigm ultimately means that alcohol-related cues and contexts can precipitate relapse - even after a prolonged period of abstinence (Ghiţă et al., 2019; Hone-Blanchet et al., 2014; Lee et al., 2007; Mellentin et al., 2017; Miranda et al., 2020; Wall et al., 2001; Zironi et al., 2006). The context-dependency of alcohol craving indicates that extinction must take place in environments similar to the context of associative learning (Conklin & Tiffany, 2002).

Another factor that impedes long-term abstinence is craving-related anxiety and its interplay with alcohol craving. In the context of the current study craving-related anxiety means anxiety that is triggered by alcohol-cues and -contexts. A network modeling analysis by Anker et al. (2019) showed that anxiety states, such as social anxiety and stress, cause and facilitate alcohol craving, which is directly involved in alcohol drinking behavioral patterns. This is because chronic alcohol abuse leads to a shift from positive to negative reinforcement in the motivational aspects of alcohol-seeking, wherefore individuals with AUD drink to experience relief from anxiety and stress (Koob et al., 2004; Sinha et al., 2009). Thus, alcohol drinking in patients with AUD is motivated by an urge to drink to cope with negative states, such as craving and craving-related anxiety. During abstinence, when individuals with AUD are exposed to alcohol-related cues and contexts, they may experience alcohol craving as well as craving-related anxiety. This craving-related anxiety state is, in return, facilitating craving (Breese et al., 2011; Duka et al., 2002; Fox et al., 2007; Haass-Koffler et al., 2014; McCaul et al., 2017; Sinha et al., 2009). Thus, it is crucial to investigate the role of craving-related anxiety in craving and AUD since it might be interfering with the recovery process and successful abstinence (Wolitzky-Taylor et al., 2018).

Cue-exposure therapy in alcohol use disorder

Based on the cue-reactivity paradigm, where contextual stimuli and environments serve as triggers for alcohol craving and craving-related anxiety, cue-exposure therapy (CET) uses repeated exposure to those cues without performing the behavioral response, drinking alcohol. The aim is to extinguish the conditioned responses (CR) from alcohol-related cues and contexts by following the principles of systematic desensitization (Doñamayor et al., 2021; Ghiţă & Gutiérrez-Maldonado, 2018; Ghiţă et al., 2019; Mellentin et al., 2017; Vollstädt-Klein et al., 2011). Systematic desensitization means that the individuals are gradually exposed to CS and therefore experience craving and craving-related anxiety. Specifically, they are prevented from drinking during this exposure but are instructed to apply relaxation exercises or other functional strategies. After repeated exposure to the alcohol-related cues and contexts without the reinforcing effects of alcohol, the levels of alcohol craving and craving-related anxiety decrease. This is called habituation (Craske et al., 2014; Doñamayor et al., 2021; Drummond & Glautier, 1994; Mellentin et al., 2017; Stamou et al., 2016). Because of this gradual approach to exposure, a hierarchy of exposure is required for each individual, on which the order of the cues and contexts is based. This hierarchy goes from the cues and contexts that induce the lowest levels of craving and anxiety to those that induce the highest levels.

Mainly, CET consists of in-vivo exposure, imagery techniques, or simulation of alcoholic beverages by presenting auditory, visual, or photographic cues (Conklin & Tiffany, 2002; Mellentin et al., 2017; Monti et al., 2006). However, CET for AUD has shown modest effectiveness, and results seem to be inconsistent. In a systematic review, Conklin and Tiffany (2002) concluded that CET is primarily conducted in a neutral and safe environment (e.g., therapy room) with only one cue present at a time, limiting the generalization of the therapy effects to other contexts and cues in real life. They criticize that how CET is implemented is not based on what is known on extinction research (e.g., context-dependency) which is a threat to the effectiveness of CET. Accordingly, CET should aim to fully extinguish cues through multiple exposures to multiple cues and contexts and should be timed optimally within and between treatment sessions to obtain the best results. Virtual reality (VR) seems to be a promising technology that enhances the effectiveness of CET and that can be used for inducing and assessing craving and anxiety in vulnerable populations (Ghiţă et al., 2018; Maples-Keller et al., 2017).

The potential of virtual reality

VR is increasingly used in psychiatric populations and has been used to assess and treat several disorders (Ferrer García & Gutiérrez Maldonado, 2012; Hone-Blanchet et al., 2014; Maples-Keller et al., 2017; Paris et al., 2011; Rothbaum et al., 2014). VR is a computer-generated simulation of the real world. This is achieved by reproducing audio, tactile, and visual stimuli from the real world by means of technology (Durl et al., 2017). With the help of head-mounted displays, gesture-sensing gloves, synthesized sounds, and vibrotactile platforms, VR involves multiple senses and allows for active exploration of and engagement with the virtual environment (Bouton et al., 2006; Gatti et al., 2008; Ghiţă & Gutiérrez-Maldonado, 2018; Ghiţă et al., 2019b; Maples-Keller et al., 2017, Spagnoli et al., 2014). It allows the developers to create environments that offer a highly immersive experience that feels real and that shut out stimuli from the actual world (Fox et al., 2009). Being exposed to complex and close-to-real-life VR environments might be beneficial regarding the context-dependency of the craving response (Conklin & Tiffany, 2002; Lebiecka et al., 2021; Trahan et al., 2019; Tsamitros et al., 2021). The sense of "really being there" and "emotional presence" might increase the effectiveness of CET as it is more similar to the real world, where individuals with AUD encounter complex environments with multiple stimuli at the same time. Therefore, VR is considered to induce greater levels of subjective and physiological craving and craving-related anxiety and thereby improves the effectiveness of CET and its ecological validity (Lee et al., 2007). This contrasts with

traditional CET, where only one cue is presented at a time in a therapy room, and extinction cannot be generalized to real-life (Conklin & Tiffany, 2002; Kwon et al., 2006).

Nevertheless, the high level of presence during VR exposure can lead to cybersickness which can interfere with the effectiveness of VR treatments, raises ethical issues, and questions the usability of VR exposure studies (Lebiecka et al., 2021; Segawa et al., 2020; Weech et al., 2019). More studies on the interplay between immersion, effectiveness, and cybersickness must be conducted (Ghiţă & Gutiérrez-Maldonado, 2018; Segawa et al., 2020; Weech et al., 2019). In their systematic review on VR in alcohol studies, Durl et al. (2017) concluded that many VR simulations lack graphical fidelity resulting in limited spatial awareness and engagement and thus, restrict the sense of presence. More attention has to be paid to the graphical quality of the VR (Durl et al., 2017). In most VR studies, different VR technologies, varying in costs, features, and quality, were used, making it difficult to compare results (Trahan et al., 2019). Although VR technology has become more affordable over the last years, the questions of cost-benefit as well as accessibility of ever-evolving VR-technologies in the clinical field have to be emphasized more (Trahan et al., 2019). Regardless of the possible threats to the application of VR in clinical contexts, previous research indicates great potential of VR as an assessment and treatment tool.

Virtual reality as an assessment tool for momentary levels of craving and anxiety

Due to the advantages of VR mentioned above, VR might have its benefits as an assessment tool for assessing individuals with AUD in close-to-real-life scenarios (Cho et al., 2008; Gatti et al., 2008; Ghiţă & Gutiérrez-Maldonado, 2018; Ghiţă et al., 2019a; Spagnoli et al., 2014). VR assessment has shown to result in higher motivation to change and self-efficacy compared to the traditional assessment. This is because the patients are actively involved in the VR-environments, receive multisensory feedback in real-time, and see their actions' effects (Bandura, 2001; Gatti et al., 2008; Riva et al., 2006; Riva & Gaggioli, 2009). Several studies have shown that VR can be used to induce and measure the momentary level of alcohol-craving and craving-related anxiety while being exposed to the VR alcohol-related environments (Bordnick et al. 2008; Ghiţă et al., 2019a; Ghiţă et al., 2021; Kim & Lee, 2015; Lee et al., 2007; Lee et al., 2008; Ryan et al., 2010). Still, only a few studies have been conducted that assessed anxiety induced by VR alcohol-cues and -contexts in patients with AUD. Those that did measure VR alcohol-cue-induced anxiety found significant evidence that VR can be used to induce and assess craving-related anxiety in patients with AUD (Ghiţă et al., 2019a; Ghiţă et al., 2019b; Ghiţă et al., 2021). To determine if and to what extent VR can be used as an assessment tool for alcohol-craving, most studies compared the craving

levels in a neutral, non-alcohol-related environment (e.g., white room with a glass of water) with the level of craving in different alcohol-related environments (e.g., bar). For example, a VR alcohol cue-reactivity assessment system (VR-ACRAS) was successfully used to induce and assess subjective alcohol-craving levels of non-treatment-seeking individuals with AUD during exposure to alcohol-related and neutral environments (Bordnick et al., 2008). The cue-induced, momentary craving levels were significantly higher in four different VR alcohol-related environments than in a neutral VR environment. Overall, research suggests that VR technology can be used to induce and assess clinically significant levels of craving, which is a prerequisite for the usefulness and effectiveness of VR as a treatment tool.

Virtual reality cue-exposure therapy

In addition to the application of VR as an assessment tool, VR seems to have the potential to improve CET for individuals with AUD, specifically to reduce alcohol craving and hence the risk of relapse, in an ecologically valid manner (Conkin & Tiffany, 2002; Ghiţă & Gutiérrez-Maldonado, 2018; Segawa et al., 2020). Multiple studies found promising results regarding the effectiveness of VR-CET on alcohol craving. Kwon et al. (2006) and Lee et al. (2007) found a significant reduction from pre-VR-CET to post-VR-CET in members of Alcoholics Anonymous, after removing three participants that had been abstinent for over a year. Further, there is evidence that VR therapy was more effective in decreasing alcohol craving than cognitive-behavioral therapy in patients with alcohol dependence (Lee et al., 2009). This was found for self-reported craving levels measured with visual analog scales (VASs) and confirmed by a physiological measure of craving. Interestingly, the magnitude of the change in craving throughout the VR sessions was higher in the alcohol-dependent group compared to a healthy control group. It has also been shown that VR therapy is effective in treating heavy social drinkers as indicated by implicit and explicit self-reported cravings (Choi & Lee, 2015).

Most studies investigating the effectiveness of VR-CET for anxiety did not focus on craving-related anxiety as employed in the current study (Maples-Keller et al., 2017; Parsons & Rizzo, 2008). Those studies that did focus on craving-related anxiety found promising results (Ghiţă et al., 2019a; Ghiţă et al., 2019b; Ghiţă et al., 2021). Although previous research findings are encouraging, various systematic reviews of VR in alcohol studies concluded that longitudinal evidence of effects, rigorous clinical trials with larger samples and control groups, and evidence for ecological validity are needed (Durl et al., 2017; Ghiţă & Gutiérrez-Maldonado, 2018; Lebiecka et al., 2021; Segawa et al., 2020; Trahan et al., 2019; Tsamitros et al., 2021). Existing studies used heterogenous VR exposure techniques,

differed in numbers of VR-exposure sessions and lengths of exposure, and included varying types of samples (e.g., social drinkers, binge drinking college students, patients with AUD) (Durl et al., 2017). Therefore, conclusions about the effectiveness of VR to decrease craving and craving-related anxiety in patients with AUD must be drawn with caution. Regardless of the limitations, the findings point to a potential of VR-CET to decrease levels of alcohol craving and craving-related anxiety.

The ALCO-VR software

The current study is part of a bigger project aiming to develop and improve a virtual reality software, the ALCO-VR software, for assessing and treating alcohol craving and craving-related anxiety in individuals suffering from AUD. After determining the cues and contexts that elicit craving (Ghiţă et al., 2019), the identified triggers of alcohol craving were used for developing the virtual environments for the ALCO-VR software. Considering the context-dependency of craving and anxiety, four alcohol-related environments (e.g., bar, at-home, restaurant, pub) were designed. Following studies showed that ALCO-VR is a valid software that can be used as an assessment (Ghiţă et al., 2019a; Ghiţă et al., 2021) and VR-CET tool for alcohol craving and craving-related anxiety (Ghiţă et al., 2019b; Hernández-Serrano et al., 2020). A case study by Ghiţă et al. (2021) is in line with those results and supports the use of VR-CET to decrease momentary levels of alcohol craving and craving-related anxiety in patients with AUD.

The current study

The ALCO-VR software was used in the current study as well. Particularly, the current study examined the momentary levels of craving and craving-related anxiety measured with visual analog scales (VASs). Those momentary levels are ecologically valid as they represent the states that individuals with AUD might face in the moment of encountering alcohol-related cues and contexts in the real world (Enkema et al., 2021; Leal et al., 2017; Serre et al., 2015; Spagnoli et al., 2014). Based on the previous findings, the current study aims at investigating the extent to which VR, specifically the ALCO-VR software, can be used to induce and assess the momentary levels of alcohol craving and craving-related anxiety during VR exposure to alcohol-related environments in patients with AUD. Similar to previous studies, this will be examined by comparing the participants' levels of craving and craving-related anxiety in the neutral, non-alcohol-related environments with those in the alcohol-related environments (Bordnick et al. 2008; Ghiţă et al., 2019a; Ghiţă et al., 2021; Kim & Lee, 2015; Lee et al., 2007; Lee et al., 2008; Ryan et al., 2010). Thereby the neutral environment, a white room with a glass of water, is used as a baseline measure of craving and

craving-related anxiety. Second, the current study aims at investigating the extent to which the ALCO-VR software can be used as a VR-CET tool to reduce the momentary levels of alcohol craving and craving-related anxiety from pre- to post-treatment assessment. The following is hypothesized:

H_{1a}: The self-reported momentary levels of alcohol-craving are lower in the baseline VR neutral environment compared to the alcohol-related environments in AUD patients at pre-VR-CET assessment.

H_{1b}: The self-reported momentary levels of craving-related anxiety are lower in the baseline VR neutral environment compared to the alcohol-related environments at pre-VR-CET assessment.

H_{2a}: The self-reported momentary levels of alcohol-craving in the alcohol-related VR environments at post-VR-CET assessment are lower compared to the pre-VR-CET assessment.

H_{2b}: There is a significant reduction in momentary levels of craving-related anxiety in the alcohol-related environments from pre-VR-CET assessment to post-VR-CET assessment in AUD patients.

Methods

Research design

A within-subject, repeated-measures design was employed. There were two independent variables. The first is *VR-environment*, with five levels (bar, restaurant, at-home, pub, neutral), and the second is *assessment* with two levels (pre-VR-CET and post-VR-CET). The dependent variables are the *self-reported levels of momentary alcohol craving* and *craving-related anxiety* during exposure to alcohol-related and neutral VR environments, measured with VASs. The Ethics Committee of the University of Barcelona and the Hospital Clinic of Barcelona have granted the ethical approval. The ethical code number is 0377 (HCB/2017/0377), and thus, the study was approved in September 2017.

Participants

Participants were recruited from the Hospital Clinic of Barcelona by the method of purposive sampling. The lead clinical psychologist chose the patients based on their clinical history while they were under ambulatory TAU at the moment of this study. Inclusion criteria were an AUD diagnosis according to the DSM-5 and being an outpatient of TAU for AUD at

the Hospital Clinic of Barcelona with a focus on patients with resistance to TAU. Resistant-to-TAU indicated that the patients experienced relapse in the first six months after finishing treatment at the Addictive Behaviours Unit of the Hospital Clinic of Barcelona. The TAU for outpatients of the Hospital Clinic of Barcelona includes pharmacotherapy and psychosocial care. Exclusion criteria were severe psychopathology and cognitive impairment, use of anti-craving medication, and pregnancy. Ultimately, 21 participants were recruited, of which four had to be excluded because of missing data. The missing data are the result of technical problems at the time of data collection. The final sample (N = 17) had a mean age of 53.12 (*SD* = 8.18) and included ten males (58.8 %) and seven females (41.2 %). Six participants (35.3%) were taking Disulfiram during the study period, which is a medication that induces negative effects, such as headache and nausea when consuming any alcohol.

Materials

Measures

Alcohol Use Disorders Identification Test. To measure the participants' alcohol misuse patterns, the Spanish version of the Alcohol Use Disorders Identification Test (AUDIT, see Appendix A) was employed (Guillamón et al., 1999). Precisely, the test consists of 10 items that assess alcohol consumption in terms of frequency and quantity ("how often do you have a drink containing alcohol"), dependence symptoms ("How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?"), and harmful consequences of consumption ("Have you or someone else been injured as a result of your drinking") (Babor et al., 2001; Saunders et al., 1993) intending to detect harmful patterns of alcohol use (Higgins-Biddle & Babor, 2018). The response options range from 0 to 4, except for items nine and ten, which can be answered with 0, 2, or 4, resulting in a final score between 0 and 40 (Babor et al., 2001). A total score equal to or higher than eight is considered to indicate hazardous and harmful alcohol consumption and possible alcohol dependence and was used as a cut-off score in the current study (Higgins-Biddle & Babor, 2018; Nadkarni et al., 2019; Reinert & Allen, 2007; Saunders et al., 1993). The AUDIT has shown to have good psychometric properties, such as high test-retest reliability and internal consistency, across various populations and languages (Alvarado et al., 2009; Lopéz et al., 2019; Meneses-Gaya et al., 2009; Meneses-Gaya et al., 2010; Nadkarni et al., 1029; Reinert & Allen, 2007).

Visual Analogue Scales. VASs are considered reliable instruments to assess self-reported, momentary levels of alcohol craving (VAS-C) (Drobes & Thomas, 1999; Kavanagh

et al., 2006; Kavanagh et al., 2013; Sung & Wu, 2018) and anxiety (VAS-A) (Sung & Wu, 2018; Williams et al., 2010) as well as clinically significant changes in the levels craving and anxiety (Kavanagh et al., 2006; Sung & Wu, 2018; Williams et al., 2010). These scales have also been employed to assess alcohol craving and craving-related anxiety during VR exposure (Bordnick et al., 2008; Ghiţă et al., 2019a; Ghiţă et al., 2021; Ryan et al., 2010). The VAS-C ranged from 0 (no craving) to 100 (intense craving). Similarly, the VAS-A ranged from 0 (no anxiety) to 100 (intense anxiety). The scores were categorized based on previous studies (Lundahl & Johanson, 2011; Reid et al., 1998; Williams et al., 2010) namely, from 0 to 25 ("not at all" craving/anxiety), from 26 to 50 ("mild" craving/anxiety), from 51 to 75 ("moderate" craving/anxiety), and from 76 to 100 ("extreme or intense" craving/anxiety).

Instruments

Hardware. Next to the Oculus Rift S head-mounted display (HMD) (Oculus VR, Irvine, CA, USA), the VR equipment consisted of sensors, touch controllers, and a computer that is compatible with the VR technology (INTEL® Core™ i7-2,600 CPU, 16.0 GB RAM, 64-bit operating system, x64 processor, NVIDIA GeForce GTX 1080 Ti graphic card).

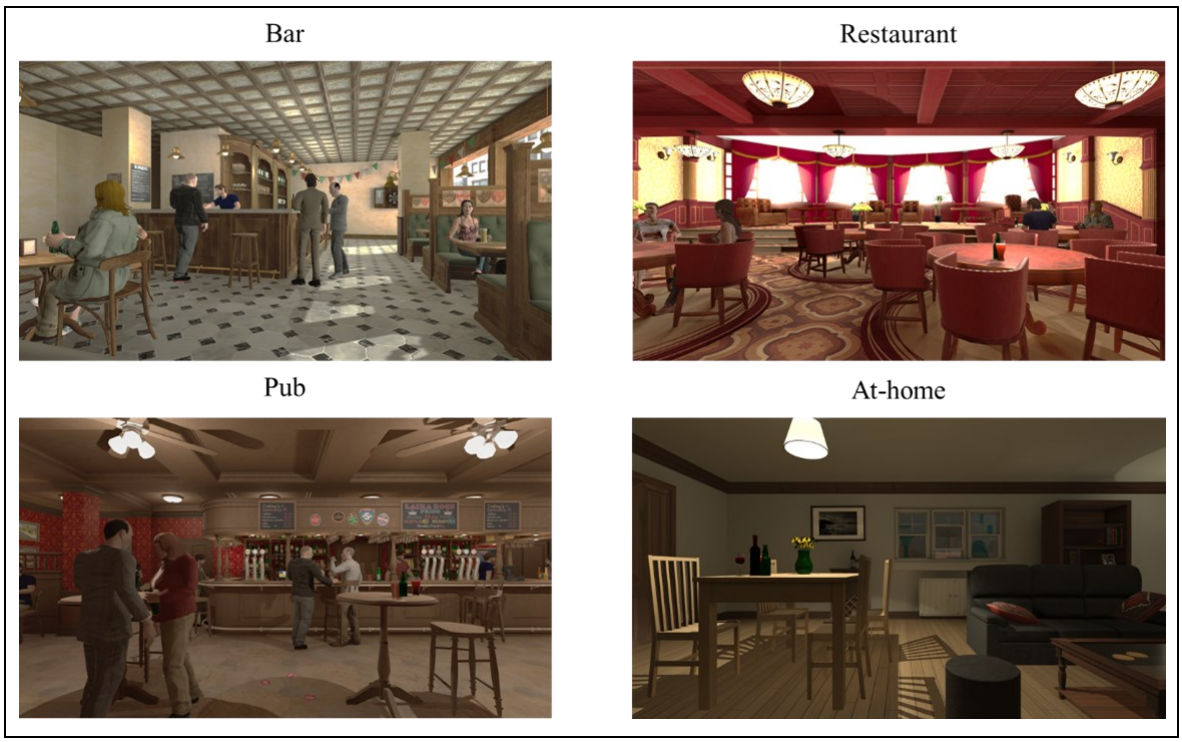
Software. The ALCO-VR software was used to assess and treat the AUD patients in the current study. It was developed by the VR-Psy Lab of the University of Barcelona, based on previous research conducted by the University. Accordingly, the ALCO-VR software included one neutral environment in the form of a white room with a glass of water, four alcohol-related environments, a bar, restaurant, pub, and at-home simulation (figure 1), and 20 different alcoholic beverages. Hence, it incorporated social interactions (with human avatars) or no social interactions and different times of the day (day- or night-time). To create a "sense of being there" for the participants and to increase ecological validity, the environments were designed to be as realistic and interactive as possible. Therefore, the software was created so that the participants could approach an alcoholic drink, or other objects in the simulations, with their hands.

The ALCO-VR software consists of two parts. The first part is the assessment part, which aims to induce and assess momentary craving and craving-related anxiety while being exposed to the VR environments. The second part is the treatment part which is used to conduct CET. In the assessment part of the ALVO-VR software, the VAS-C and VAS-A were used to determine a hierarchy of exposure to allow for gradual exposure. The hierarchy went from the lowest-rated environment with the lowest-rated alcoholic beverage to the

highest-rated environment with the highest-rated drink. This resulted in each participant's five most preferred drinks, which were considered for the treatment part of the ALCO-VR software. Thus, the VR-CET was tailored to each participant and included prolonged exposure to the cues and contexts based on each participant's subjective craving ratings.

Figure 1

Images of the alcohol-related ALCO-VR-environments shown to the participants



Procedure

After the lead clinical psychologist had selected the patients based on the abovementioned inclusion criteria, they were invited to participate in the current study. When they had signed the written informed consent, an appointment was scheduled for the initial assessment session. The whole study for each participant lasted approximately five weeks and consisted of eight sessions, namely, one pre-VR-CET assessment, six VR-CET booster sessions, and one post-VR-CET assessment session (figure 2). The current study is only considering the data obtained during the initial and final assessment sessions.

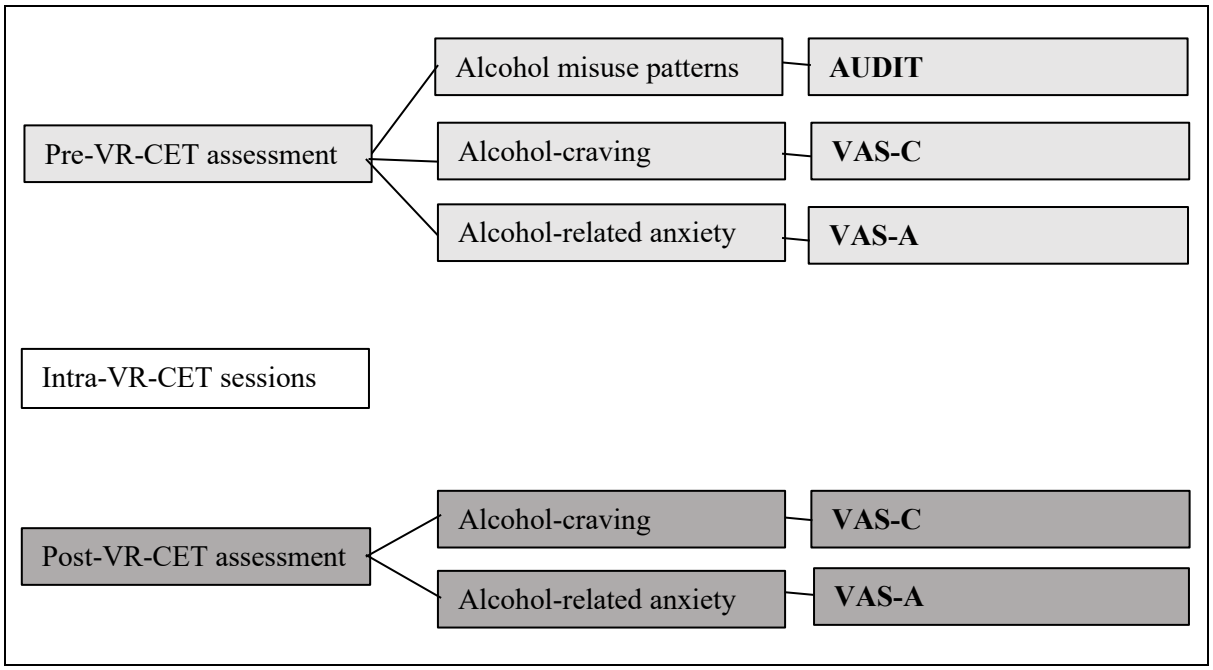
During the initial assessment session, the participants provided sociodemographic information, such as dual pathology, medication, and abstinence in days before assessment session and filled in the AUDIT. This was followed by the ALCO-VR assessment in which the momentary levels of craving and craving-related anxiety were measured with the VAS-C

and VAS-A. Within this VR assessment, the participants were first entering a neutral white room with a glass of water to have a baseline measure of their momentary levels of craving/anxiety. At the same time, the participants could get used to the VR equipment. After that, the four alcohol-related VR environments and 20 alcoholic beverages were presented while the participants had to indicate their momentary levels of craving/anxiety on the VASs every 20 seconds. This resulted in 20 craving and 20 anxiety ratings (4 environments x 5 drinks = 20 ratings x 2 (craving and anxiety) = 40 ratings). The exposure hierarchy could be established based on those outcomes, which was then used in the VR-CET sessions. To make the exposure experiences as immersive as possible, olfactory stimuli, in the form of alcohol-soaked cotton pads corresponding to the virtual drinks presented, were placed close to the participants. In the end, the participants were also asked to indicate their perceived realism of the environments and drinks on a scale from 0 to 10. The final assessment session was similar but without completing the AUDIT and was scheduled approximately three days after the final VR-CET session.

The six VR-CET sessions, lasting approximately 50 minutes, were conducted with the treatment part of the ALCO-VR software and took place two times a week for three consecutive weeks. They were completed in addition to the participants' TAU. The VR-CET treatment session did not include any other therapeutic methods beyond cue exposure which means that the sessions consisted of exposure and response prevention, based on the principles of systematic desensitization and habituation. The participants were instructed to touch and observe the alcoholic stimuli from all angles without attempting to (virtually) drink from it. The sessions were conducted by experienced practitioners from the Hospital Clinic of Barcelona. Each session ended with a debriefing in which the participants could disclose any thoughts, emotions, and behaviors related to consuming alcohol to minimize the risk of relapse. Although the treatment sessions are shortly described to gain an overview of what was done, the data obtained during the treatment sessions were not considered in the analyses of the current study.

Figure 2

Outline of the study protocol that the participants underwent



Data Analysis

All analyses were performed with the Statistical Package for Social Sciences (SPSS, 27th version), and one- and two-tailed tests with a p-value of 0.05 were used. First, to test whether the scores on the VASs and AUDIT are normally distributed, Shapiro-Wilk tests were employed and supported by QQ-plots and histograms (see Appendix A). Accordingly, the assumption of normality of data was not satisfied, p-values < 0.05, wherefore non-parametric tests were applied in this study. Second, descriptive statistics provided the medians, means, and standard deviations of the baseline measures and sociodemographic variables.

Third, Friedman's ANOVA was used to compare the level of craving/anxiety in the neutral environment with the level of craving/anxiety in the four alcohol-related environments at pre-VR-CET. To see which environment is superior in triggering the highest level of craving/anxiety, post-hoc Wilcoxon signed-rank tests were applied to compare the level of craving/anxiety in the neutral environment with each alcohol-related environment separately (H_{1a}, H_{1b}).

Fourth, to examine whether there is a significant reduction in the levels of craving/anxiety from pre- to post-VR-CET assessment, Friedman's ANOVA was used. This was done with each alcohol-related environment separately, as well as with the overall mean level of craving/anxiety in the four alcohol-related environments. Lastly, for the overall craving/anxiety mean, levels of change were established using the categories for craving/anxiety. Participants can move one level up or down (from "moderate"

craving/anxiety to "mild" craving/anxiety), two (from "intense" to "mild"), three (from "intense" to "no at all"), or no level up or down (H_{2a}, H_{2b}). For all tests, the effect sizes were calculated to get an indication of the strengths of the effects. Thereby, effect sizes below 0.3 are considered small effects, below 0.5 medium, and above 0.5 large effects (Cohen, 1988).

Results

Normality testing

According to the Shapiro-Wilk test, the AUDIT scores, W(17) = .926, p = .184, and the craving-related anxiety scores (VAS-A at T0) in the alcohol-related environments at pre-VR-CET, W(17) = 0.946, p = .391, were considered normally distributed. All other independent and dependent variables did not meet the assumption of normality, p-values < .05. The outcomes of the Shapiro-Wilk tests were supported by histograms and QQ plots (see Appendix B), wherefore, non-parametric tests were employed.

Baseline characteristics of the sample

The sample (N = 17) showed an average AUDIT score of 16.53 (SD = 10). The AUDIT scores range from a total of 2 to 38, with a median of 14. Three of the participants scored below the cut-off score of eight, indicating that those participants did not display signs of harmful or hazardous alcohol consumption and alcohol dependence. The participants had been abstinent for an average of 81 days (SD = 100.46). The days of abstinence ranged from 3 to 360 days, with a median of 39 days, showing the high variance in the days of abstinence in the sample. Overall, the "perceived realness" of the virtual environments (M = 8.00, SD = 1.45) and the virtual drinks (M = 6.59, SD = 1.87) was rated as high, and thus, the ALCO-VR environments and drinks seem to be similar to the cues and contexts in the real world. Six participants (35.3%) were taking Disulfiram during the study period.

At pre-VR-CET, in the neutral environment, the participants reported levels of craving (M = 15, SD = 25.47) below the cut-off score of 25 ("not at all" craving) with a median of 0.00. Similarly, the levels of craving-related anxiety in the neutral, non-alcohol-related environment (M = 27.00, SD = 25.96) mainly ranged from no to mild anxiety, with a median of 19. In the alcohol-related environments, the overall mean level of craving was 48.46 (SD = 27.44), with a median of 61.25. Eleven Participants (64.7%) reported moderate or intense levels of alcohol craving. The overall mean level of anxiety was 45.98 (SD = 24.18), with a median of 50. Eight participants (47.1%) reported moderate or intense levels of anxiety. All descriptive statistics of the demographic variables as well as of the levels of

craving and anxiety in each of the four alcohol-related environments at baseline are displayed in table 1.

Table 1

Characteristics of participants at initial assessment.

Characteristics	**N (%) or Mean ± SD**	**Median [Min, Max]**
Age	53.12 ± 8.17	
Gender (male)	7 (41.2%)	
Education		
Secondary school education	2 (11.8%)	
Highschool	2 (11.8%)	
Post-high school education	5 (29.4%)	
Bachelor's degree	7 (41.2%)	
Master's degree	1 (5.9%)	
Socioeconomic status		
Low	3 (17.6%)	
Medium	13 (76.5%)	
High	1 (5.9%)	
Civil status		
Single	2 (11.8%)	
Married/in a relationship	6 (35.3%)	
Separated/divorced	7 (41.2%)	
Widower	2 (11.8%)	
Psychiatric comorbidity	9 (52.9%)	
Current smoking	12 (70.6%)	
Disulfiram (Antabuse)	6 (35.3%)	
AUDIT	16.53 ± 10.89	14 [2, 38]
Abstinence in days	80.71 ± 100.46	39.00 [3, 360]
Perceived realism VR environments	8 ± 1.46	9 [6, 10]
Perceived realism VR drinks	6.58 ± 1.87	7 [3, 9]
Anxiety neutral environment	27.00 ± 25.96	19 [0, 70]
Craving neutral environment	15 ± 25.47	0 [0, 84]
Anxiety alcohol-related environments	45.99 ± 24.18	50 [8.25, 88,50]
Anxiety at-home	43.81 ± 27.84	42 [0, 93]
Anxiety bar	46.59 ± 25.99	50 [4, 89]
Anxiety restaurant	44.84 ± 21.73	50 [8, 86]
Anxiety pub	48.75 ± 24.61	54.20 [0, 95]
Craving alcohol-related environments	48.45 ± 27.43	61.25 [0.25, 88.75]
Craving at-home	48.94 ± 27.29	58 [0, 96]
Craving bar	47.39 ± 28.30	58 [0, 87]
Craving restaurant	47.05 ± 27.73	58 [0, 87]
Craving pub	50.46 ± 29.19	61 [1, 94]

ALCO-VR as an assessment tool

Regarding momentary levels of alcohol-craving on the VAS-C at baseline (T0), Friedman's ANOVA revealed a statistically significant difference across the VR environments, $\chi^2(4) = 20.25$, $p < 0.001$ (H_{1a}). As expected, post-hoc Wilcoxon signed rank test showed significant differences between the neutral and at-home environment ($z = 3.054$, $p = 0.002$, $r = 0.524$), between neutral and bar ($z = 3.195$, $p = 0.001$, $r = 0.548$), between neutral and restaurant ($z = 3.103$ $p = 0.002$, $r = 0.532$), and between neutral and pub ($z = 3.196$, $p = 0.001$, $r = 0.548$). Similarly, Friedman test showed a significant difference across the VR environment regarding the momentary levels of craving-related anxiety on the VAS-A at baseline (T0), $\chi^2(4) = 9.570$, $p = 0.041$ (H_{1b}). Specifically, Wilcoxon signed rank tests indicated significant difference between the neutral and bar environment ($z = 2.224$, $p = 0.026$, $r = 0.381$), between neutral and restaurant ($z = 2.430$, $p = 0.015$, $r = 0.417$) and between neutral and pub ($z = 2.500$, $p = 0.012$, $r = 0.429$). Against expectation, there was no significant difference between the level of craving-related anxiety in the neutral and at-home environment ($z = 1.903$, $p = 0.057$, $r = 0.326$).

ALCO-VR as a treatment tool

As expected, Friedman's ANOVA showed a significant decrease in the levels of momentary alcohol-craving from pre- (T0) to post-VR-CET (T1) assessment (Mdn = 6.00), $\chi^2(1) = 7.118$, $p = 0.008$ (H_{2a}). Regarding the momentary levels of craving-related anxiety, the analysis revealed that the level of anxiety at post-VR-CET (Mdn = 7.25) is significantly lower than at pre-VR-CET assessment, $\chi^2(1) = 9.941$, $p = 0.002$ (H_{2b}). Specifically, five participants (29.4%) showed no improvement in their levels of craving, three participants (17.6%) moved one level down, seven (41.2%) moved two levels down, and one individual (5.9%) moved three levels down from extreme craving to no craving. One participant's levels of craving increased two levels from no to moderate craving. With regards to craving-related anxiety, four participants (23.5%) showed no improvement in their levels of anxiety, seven participants' scores (41.2%) decreased one level, four participants' scores (23.5%) decreased two levels, and one participant's scores (5.9%) decreased three levels from extreme to no anxiety. The same individual who showed increased craving levels at post-VR-CET also reported increased craving-related anxiety levels at post-VR-CET. Whereas at pre-VR-CET 23.5% of the participants had no alcohol-craving and no craving-related anxiety, 70.6% had no craving and no craving-related anxiety at post-VR-CET (H_{2a}, H_{2b}). The categorical levels of craving and anxiety at post- compared to pre-VR-CET can be found in table 2.

Table 2

Categories of craving and craving-related anxiety at pre-VR-CET compared to post-VR-CET

	Pre-VR-CET (T0)		Post-VR-CET (T1)	
	N	%	N	%
Craving				
Not at all	4	23.5	12	70.6
Mild	2	11.8	2	11.8
Moderate	9	52.9	3	17.6
Intense	2	11.8		
Anxiety				
Not at all	4	23.5	12	70.6
Mild	5	29.4	4	23.5
Moderate	6	35.3	1	5.9
Intense	2	11.8		

The results are further supported when examining the levels of craving and craving-related anxiety at pre- and post-VR-CET in each alcohol-related environment separately (table 3). Namely, Friedman's ANOVA revealed that the levels of anxiety at post-VR-CET were significantly lower compared to pre-VR-CET in the at-home environment ($\chi^2(1) = 7.118$, $p = 0.008$), in the bar environment ($\chi^2(1) = 13.235$, $p = 0.000$), in the restaurant environment ($\chi^2(1) = 7.118$, $p = 0.008$), as well as in the pub environment ($\chi^2(1) = 12.250$, $p = 0.000$). Regarding craving, Friedman tests showed that the levels of craving at post-VR-CET were significantly lower compared to pre-VR-CET in the at-home environment ($\chi^2(1) = 7.118$, $p = 0.008$), in the bar environment ($\chi^2(1) = 9.000$, $p = 0.003$), in the restaurant environment ($\chi^2(1) = 6.250$, $p = 0.012$) and in the pub environment ($\chi^2(1) = 7.118$, $p = 0.008$).

Table 3

Differences in craving-related anxiety (VAS-A) and alcohol craving (VAS-C) self-reports from pre- (T0) to post-VR-CET (T1).

	Pre-VR-CET (T0)			Post-VR-CET (T1)			
	Mean (SD)	Median	IQR[a]	Mean (SD)	Median	IQR	χ^{2b}
At home							
Anxiety	43.81 (27.84)	42.00	47	15.65 (22.01)	5.00	34	7.118***
Craving	48.94 (27.29)	58.00	38	19.59 (24.17)	7.00	35	12.250***
Bar							

Anxiety	46.59 (25.99)	50.00	37	15.59 (19.98)	6.00	25	13.235***
Craving	47.39 (28.30)	58.00	55	18.47 (21.36)	7.00	29	9.000***
Restaurant							
Anxiety	44.84 (21.73)	50.00	35	16.65 (20.99)	13.00	28	7.118***
Craving	47.05 (27.73)	58.00	48	19.88 (24.10)	7.00	34	6.250*
Pub							
Anxiety	48.75 (24.16)	54.20	37	15.35 (19.42)	6.00	29	12.250***
Craving	50.46 (29.19)	61.00	44	18.76 (21.73)	7.00	32	7.118***

[a]IQR, interquartile range; [b]Friedman's ANOVA; *** $p < .001$; * $p < .05$.

Discussion

The current study is part of a bigger project that aims to examine the effectiveness of a VR-software, namely ALCO-VR, as an assessment and treatment tool for resistant-to-TAU individuals suffering from AUD. Thereby, the focus was laid upon alcohol craving, and craving-related anxiety as both are considered to interfere with abstinence maintenance after treatment which remains to be a significant issue (Addolorato et al., 2001; Breese et al., 2011; Campbell et al., 2018; Degenhardt et al., 2017; Fox et al., 2007; Haass-Koffler et al., 2014; Kwon et al., 2006; McCaul et al., 2017; NIDA, 2012, WHO, 2019; Wolitzky-Taylor et al., 2018; Zironi et al., 2006). First, the current study aimed at investigating the extent to which the ALCO-VR software can be used to induce and assess momentary levels of craving and craving-related anxiety during VR exposure to alcohol-related environments. Overall, the findings of the current study supported that the ALCO-VR software can be used to induce and assess craving (H_{1a}) and anxiety (H_{1b}) in patients with AUD. As expected, the self-reported momentary levels of alcohol craving and craving-related anxiety were significantly higher in the VR alcohol-related environments compared to the VR neutral environment. One exception was found regarding the neutral and at-home environment regarding the levels of anxiety. Second, the current study aimed at investigating the extent to which the ALCO-VR software can be used as a VR-CET tool to reduce the momentary levels of alcohol craving and craving-related anxiety from pre- to post-treatment assessment. The current study's findings suggest that the ALCO-VR software can be used as a VR-CET tool when applied as a booster treatment next to TAU. In line with expectations, the levels of alcohol craving (H_{2a}) and craving-related anxiety (H_{2b}) were significantly lower at the final assessment compared to the initial assessment. Interestingly, approximately two-thirds of the participants showed a

reduction of craving and anxiety, whereas the rest showed no improvement. One participant's craving and anxiety got worse throughout the study. The current study was one of the first clinical trials following the CONSORT guidelines for clinical research and investigated the effectiveness of VR on assessing and reducing self-reported momentary levels of craving and craving-related anxiety in resistant-to-TAU patients with AUD.

The current findings in the light of previous research

The results are consistent with previous research and confirm the effectiveness of the ALCO-VR software as an assessment and treatment tool in patients with AUD who are resistant to TAU. The findings are in line with previous studies showing that craving and anxiety are higher in the alcohol-related environments compared to the neutral environment, mostly a white room with a glass of water (Bordnick et al., 2008; Cho et al., 2008; Gatti et al., 2008; Ghiţă & Gutiérrez-Maldonado, 2018; Ghiţă et al., 2019a; Lee et al., 2007; Ryan et al., 2010; Spagnoli et al., 2014). This indicates that VR-alcohol-environments and -drinks can induce alcohol-craving and craving-related anxiety. At the same time, VR technology is a platform for assessing craving levels with the help of VASs. The induction of craving and craving-related anxiety by the use of alcohol-related cues and contexts are based on the cue-reactivity paradigm, and implicitly, the context-dependency of learned responses (Craskte et al., 2014; Doñamayor et al., 2020; Drummond & Glautier, 1994; Mellentin et al., 2017; Miranda et al., 2020; Paris et al., 2011; Stamou et al., 2016; Vollstädt-Klein et al., 2011). VR-environments are more effective in inducing craving and anxiety than traditional exposure methods (e.g., exposure to a bottle of alcohol in a clinical setting) because they include many stimuli at the same time (e.g., simulations of daily-life situations like a pub or bar) (Campbell et al., 2018; Conklin & Tiffany, 2002; Ghiţă & Gutiérrez-Maldonado, 2018; Mellentin et al., 2017). Additionally, VR-environments and -cues have the advantage that they are similar to the patients' real-life encounters with alcohol-related cues and contexts. Thus, they can be used to assess craving/anxiety in an ecologically valid manner. The VR technology allows to include multiple senses and is designed to be as engaging as possible and, therefore, creates a highly immersive experience (Cho et al., 2008; Ghiţă & Gutiérrez-Maldonado, 2018; Gatti et al., 2008; Lee et al., 2007; Maples-Keller et al., 2017; Paris et al., 2011, Spagnoli et al., 2014). This was indicated by the participants in the current study that rated the VR environments and -drinks as highly real. Nevertheless, high immersion could lead to simulation sickness which give rise to ethical issues and poses a threat to the applicability of VR. More research has to investigate the relation between immersion, cybersickness, and

effectiveness of VR-CET (Ghiţă & Gutiérrez-Maldonado, 2018; Lebiecka et al., 2021). A further advantage of the close-to-real-life experience offered by VR technology is that it induces higher levels of craving and anxiety compared to traditional exposure techniques and, therefore, increases the effectiveness of CET (Lee et al., 2007; Simon et al., 2020; Riva et al., 2006). Importantly, the high level of immersion and the higher levels of craving and craving-related anxiety induced in individuals with severe alcohol dependence could give rise to ethical concerns. Attention has to be paid to potential side-effects of VR exposure and specific guidelines for conducting VR-CET are required to ensure ethically justifiable use.

One unexpected finding of the current study was that the levels of anxiety in the at-home environment were not significantly higher than in the neutral environment. However, means point in the expected direction. Whether an environment induces craving and craving-related anxiety might be related to the individual's past experiences with their alcohol drinking. For example, Ghiţă et al. (2019) found that women experience greater cravings in scenarios in which they drink alone than men. Nevertheless, women did not differ in their levels of craving in the at-home environment (Ghiţă et al., 2019). At the same time, it could be that the VR at-home environment is too different from the actual homes of the participants and, thus, are too different from the context in which the craving and craving-related anxiety response was learned. The design of the other environments can be more flexible as one knows more than one pub, restaurant, and bar. According to Bouton et al. (2006) and Doñamayor et al. (2021), cues and contexts which are too different from the original learning context might not induce craving. This points towards a need for more tailored VR cues and contexts (e.g., exposure hierarchy of VR environments). In the current study the individual drinks and exposure hierarchies reflect a start for more tailored CETs. Additionally, the environments and drinks were designed based on previous research identifying the triggers for alcohol craving in individuals with AUD (Ghiţă et al., 2019). On the other hand, more research is required that examines the cues and contexts that trigger alcohol craving and craving-related anxiety prior to designing various VR environments. Trahan et al. (2019) criticises that only few studies conducted prior prototyping and included the target user, hence, individuals suffering from AUD. At the same time, more tailored VR environments make it difficult to compare VR studies because of heterogenous VR environments (Trahan et al., 2019). Regardless of the non-significant difference between the at-home and the neutral environment, the anxiety levels significantly decreased over the study period.

The findings of the current study are in line with previous research that has shown that VR-CET is effective in reducing alcohol-craving and craving-related anxiety (Choi &

Lee, 2015; Ghiţă & Gutiérrez-Maldonado, 2018; Ghiţă et al., 2019a; Ghiţă et al., 2019b; Ghiţă et al., 2021; Kwon et al., 2006; Lee et al., 2007; Lee et al., 2009; Segawa et al., 2020). The reduction of craving and anxiety is considered to be based on systematic desensitization to alcohol-related cues and contexts (Craske et al., 2014; Doñamayor et al., 2020; Drummond & Glautier, 1994; Mellentin et al., 2017; Miranda et al., 2020; Paris et al., 2011; Stamou et al., 2016; Vollstädt-Klein et al., 2011). Gradual exposure with response prevention, systematic desensitization, lead to habituation of the craving and anxiety response towards alcoholic cues and contexts (Grissom & Bhatnagar, 2009). The fact that participants were exposed to different alcohol-related environments, displaying different times of the day, different levels of social interaction, and different alcoholic cues, is contributing to the generalizability of extinction to the real world and its various alcohol-related cues and contexts (Conklin & Tiffany, 2002; Litt et al., 2000). The abovementioned advantages of VR environments are following suggestions by Conklin and Tiffany (2002) to improve the effectiveness of VR exposure. Because the alcoholic cues were presented in diverse environments similar to the original conditioning context, the generalizability of extinction is increased (Conklin & Tiffany, 2002; Segawa et al., 2020; Stasiewicz et al., 2007).

By decreasing the levels of craving and anxiety as a response to alcohol-related cues, it is aimed at reducing the risk of relapse. Several studies have confirmed that craving, as well as craving-related anxiety, are impeding abstinence maintenance (Addolorato et al., 2001; Breese et al., 2011; Campbell et al., 2018; Degenhardt et al., 2017; Fox et al., 2007; Haass-Koffler et al., 2014; Kwon et al., 2006; McCaul et al., 2017; Wolitzky-Taylor et al., 2018; Zironi et al., 2006). Nevertheless, in the current study, it was not examined whether the extinction of the craving- and anxiety-response holds in the long run and the real world or whether reduced craving and anxiety are related to a reduced risk of alcohol drinking and, thus, relapse. A few studies investigating the relationship between craving and abstinence maintenance in daily life reported no association between craving and alcohol use over subsequent hours (Cooney et al., 2009; Holt et al., 2012) and at a six-month follow-up (Krahn et al., 2005). The findings of Kaysen et al. (2014) indicated a positive correlation between craving and next hours of alcohol use. Notably, the virtual environments of the ALCO-VR software were designed based on triggers that have shown to induce craving in individuals with AUD who are resistant to treatment (Ghiţă et al., 2019). Although craving and craving-related anxiety represent essential mechanisms for abstinence maintenance, it has to be investigated whether VR-CET can be applied as a stand-alone study or as a booster treatment to reach the ultimate goal of preventing relapses.

It is also unclear whether extinction of craving and craving-related anxiety in response to alcohol cues and contexts holds in the real word of the patients. Bouton et al. (2006) named the renewal effect as a risk factor for the generalizability of extinction to the cues and contexts in the real world. Being exposed to contexts other than the extinction context could lead to a recovery of the craving and anxiety response. Accordingly, during extinction the conditioned responses craving and craving-related anxiety are not unlearned but new learning occurs where alcohol cues and contexts do not trigger craving and craving-related anxiety. The new inhibitory response is triggered by cues and contexts present during exposure but craving and craving-related anxiety are still triggered in other contexts. Still, the authors suggest that extinction is not completely context-dependent and that a generalization between contexts is possible (Bouton et al., 2006; Doñyamor et al., 2021). Longitudinal studies are required to test whether extinction of craving and craving-related anxiety holds in the real world and remains intact over time.

Interestingly, not all participants in the current study reported moderate or intense craving at baseline in the alcohol-related environments, although they have experienced several relapses in the past (Hernandez-Serrano et al., 2020). This questions the effectiveness of the ALCO-VR software in inducing craving and craving-related anxiety in patients with AUD. However, individual differences could account for the "no" to "mild" craving and anxiety scores at baseline. For example, the lengths of abstinence periods and the AUDIT scores could be related to the craving/anxiety scores at baseline. Namely, some of the participants have been abstinent for a longer time, up to 360 days, and thus, alcohol-cues do no longer induce craving in those patients. Similarly, Lee et al. (2007) and Kwon et al. (2006) found a significant reduction in craving after VR-CET when excluding patients that had been abstinent for more than a year. Further, three participants in the current study reported low AUDIT scores and are therefore not considered to have performed hazardous, harmful drinking and are not showing dependence symptoms the week before the start of participation. This is in line with Lee et al. (2007), Litt et al. (2000), and Kwon et al. (2006), who found that heavy drinkers with higher dependence symptoms report higher levels of craving when exposed to alcohol-related cues. Another possible explanation could be that for those individuals who reported "no" to "mild" alcohol-craving levels, craving did not play a significant role in their past failed abstinence attempts. An earlier study by Litt et al. (2000) showed that a third of AUD patients did not report craving when exposed to alcohol-related cues. Further, the "no" to "mild" levels of craving and craving-related anxiety at baseline could be related to individual differences in alcohol expectancies. Suzuki et al. (2020) found

that negative alcohol expectancies are related to effective regulation of craving, as individuals with AUD can reduce cue-induced craving by using cognitive strategies. Next to negative alcohol expectancies, impulsivity and perceived availability of alcohol seem to explain why some individuals report “no” to “mild” craving and anxiety when exposed to alcohol-cues (Papachristou et al., 2012). Specifically, more impulsive patients who perceive alcohol to be unavailable demonstrate no significant levels of craving while being exposed to alcohol-cues and -contexts because perceived availability has to be a necessary component of the CS complex. Although VR environments are a good platform to overcome this limitation of cue exposure because they make the participants believe that alcohol is present, participants could still be aware that no actual alcohol will be available (Murray, 2020). Indeed, the perceived realism of the drinks was a bit lower than of the environments in the current study. The abovementioned explanations could indicate that for those individuals who reported "no" to "mild" levels of craving/anxiety at baseline, the ALCO-VR-environments and cues did not induce craving or craving-related anxiety. This raises the question of whether there are individual factors related to how effectively a VR environment can induce craving/anxiety.

Generally, previous studies found individual factors such as negative alcohol expectancies, impulsivity, perceived availability of alcohol, and days of abstinence that might be related to an individual's level of craving and craving-related anxiety at baseline (Bernard et al., 2021; Lee et al., 2007; Papachristou et al., 2012; Suzuki et al., 2020). Those individual differences are important as they might also affect the effectiveness of VR-CET on craving and craving-related anxiety levels. Especially because higher levels of craving and anxiety at baseline are related to higher effectiveness of VR-CET (Lee et al., 2007). The results of the current study support that there might be differences regarding the effectiveness of VR-CET. Namely, one individual's levels of craving and anxiety increased throughout the study, and some individuals reported no change. The latter cases might be related to the baseline levels of craving and anxiety. Those individuals who did not improve already reported "no" craving/anxiety at baseline. Thus, there was no room for improvement. Additionally, Pericot-Valverde et al. (2015) found that younger age, cigarettes smoked per day, higher levels of delay discounting, and higher depression levels were associated with greater decreases in craving in treatment-seeking smokers. Thus, it seems that certain individual characteristics may benefit most from interventions aimed at reducing craving through VR-CET. However, it is uncertain why one individual's anxiety and craving levels increased over the course of the study period. When taking a closer look at that particular individual, there are no apparent patterns visible that stand out and could explain this development. Next to the four

individuals that did not improve, the other 15 participants did show reduced craving and anxiety levels. Those individuals differed in their demographic variables such as dual pathology, gender, socioeconomic status, and Disulfiram and the perceived realism of the VR drinks and environments. Thus, there are no clear patterns in demographic variables explaining why those individuals' scores were reduced. Taken together with the aforementioned individual differences in the levels of cue-induced craving and anxiety and the effectiveness of VR-CET, further clinical trials with a larger sample size are required.

Strengths and limitations

Next to the general advantages of the fully immersive experiences of the VR environments, their potential to use VASs to assess momentary levels of craving and anxiety adds to the ecological validity of the current study. Momentary levels represent the states that individuals with AUD might face when confronted with similar alcohol-related environments and cues in the real world (Enkema et al., 2021; Leal et al., 2017; Serre et al., 2015; Spagnoli et al., 2014). Next, the individuals were exposed to four different alcohol-related environments (at home, bar, restaurant, pub) designed based on previous research looking into triggers of alcohol-craving (Ghiţă et al., 2019). The VR environments included different levels of social interaction, different times of the day (at day- or night-time), and different alcoholic beverages tailored to each participant's exposure hierarchy. This leads to a variety of different contexts with tailored drinks, which adds to the generalizability of VR-CET effects to the real world, and thus to the ecological validity (Bouton et al., 2006; Conklin & Tiffany, 2002; Doñyamor et al., 2021; Ghiţă et al., 2018; Maples-Keller et al., 2017). Another strength of the current study is that participants were diagnosed with AUD who are considered resistant to TAU. Earlier studies have shown that individuals with AUD differ in their levels of cravings and anxiety compared to social or occasional drinkers (Ghiţă et al., 2019b; Lee et al., 2007).

The current findings have to be interpreted in light of some limitations. First, the small sample size makes it challenging to look into individual differences that might be important concerning the effectiveness of the ALCO-VR software in assessing and treating individuals with AUD. At the same time, it is difficult to draw solid conclusions regarding the effectiveness of the ALCO-VR software. However, found effects point towards VR-CET being a suitable booster-treatment for individuals with AUD. Second, the characteristics of some participants might have interfered with the results, as some participants had been abstinent for up to a year or reported low alcohol dependence scores (AUDIT). However,

levels of craving might differ with severity of dependence and with lengths of abstinence. Although craving levels have shown to resist over longer periods (Hone-Blanchet et al., 2014; Mellentin et al., 2017; Miranda et al., 2020; Zironi et al., 2006), some studies have indicated that craving levels are temporary and decrease with increasing lengths of abstinence (Ceccarini et al., 2020; Herrold et al., 2017). Notably, exposing highly dependent and shortly abstinent individuals to close-to-real life alcohol cues and contexts raises ethical questions that have to be further examined. Third, the craving and anxiety response includes physiological arousal wherefore, self-reports of craving, without additional physiological measures such as eye-movement activity and brain activity, might not be sufficient predictors of relapse (Lee et al., 2007; Tsamitros et al., 2021). Lastly, the ALCO-VR environments and cues are designed based on typical restaurants, bars, and pubs that can be found in Spain. Due to the high context-dependency of craving and craving-related anxiety, this could limit ALCO-VR application in other populations.

Conclusion

In conclusion, the ALCO-VR software seems to be an appropriate tool for inducing and assessing momentary levels of alcohol craving and craving-related anxiety in individuals with AUD, as well as a tool to conduct VR-CET. First, apart from the at-home environment, the alcohol-related environments induced higher levels of anxiety compared to the neutral environment. Regarding craving, the participants reported higher levels of craving in all alcohol-related environments. Second, the levels of craving and anxiety were significantly reduced from the initial to the final assessment in all four environments, after six VR-CET booster sessions. Although the overall VR-CET effect was significant, there were some differences between individuals. Due to the advantages of VR technology and the careful design of the VR environments, the current study adds to the generalizability of extinction and the ecological validity of the findings. Future research has to examine whether the reduced levels of craving and craving-related anxiety indeed decrease the risk of relapse in the real world through longitudinal data. Further, individual differences that influence the levels of cue-induced craving and anxiety and the effectiveness of VR-CET have to be investigated.

References

Addolorato, G., Leggio, L., Abenavoli, L., Gasbarrini, G., & Alcoholism Treatment Study Group. (2005). Neurobiochemical and clinical aspects of craving in alcohol addiction: a review. *Addictive behaviors*, *30*(6), 1209-1224. https://doi.org/10.1016/j.addbeh.2004.12.011

Alvarado, M. E., Garmendia, M. L., Acuña, G., Santis, R., & Arteaga, O. (2009). Assessment of the alcohol use disorders identification test (AUDIT) to detect problem drinkers. *Revista medica de Chile*, *137*(11), 1463-1468. DOI: /s0034-98872009001100008

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. Arlington, VA: American Psychiatric Publishing.

Anker, J. J., Kummerfeld, E., Rix, A., Burwell, S. J., & Kushner, M. G. (2019). Causal network modeling of the determinants of drinking behavior in comorbid alcohol use and anxiety disorder. *Alcoholism: clinical and experimental research*, *43*(1), 91-97. https://doi.org/10.1111/acer.13914

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2001). The alcohol use disorders identification test: Guidelines for use in. *World Health Organization.* Retrieved from https://apps.who.int/iris/handle/10665/67205

Bandura, A. (2001). Social cognitive theory: An agentic perspective. *Annual review of psychology*, *52*(1), 1-26. https://doi.org/10.1146/annurev.psych.52.1.1

Bernard, L., Cyr, L., Bonnet-Suard, A., Cutarella, C., & Bréjard, V. (2021). Drawing alcohol craving process: A systematic review of its association with thought suppression, inhibition and impulsivity. *Heliyon*, *7*(1). https://doi.org/10.1016/j.heliyon.2020.e05868

Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, *71*(8), 670. https://doi.org/10.1037/amp0000059

Bouton, M. E., Westbrook, R. F., Corcoran, K. A., & Maren, S. (2006). Contextual and temporal modulation of extinction: behavioral and biological mechanisms. *Biological Psychiatry*, *60*(4), 352-360. https://doi.org/10.1016/j.biopsych.2005.12.015

Breese, G. R., Sinha, R., & Heilig, M. (2011). Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. *Pharmacology & Therapeutics*, *129*(2),

149-171. https://doi.org/10.1016/j.pharmthera.2010.09.007

Campbell, E. J., Lawrence, A. J., & Perry, C. J. (2018). New steps for treating alcohol use disorder. *Psychopharmacology*, *235*(6), 1759-1773. https://doi.org/10.1007/s00213-018-4887-7

Ceccarini, J., Leurquin-Sterk, G., Crunelle, C. L., de Laat, B., Bormans, G., Peuskens, H., & Van Laere, K. (2020). Recovery of decreased metabotropic glutamate receptor 5 availability in abstinent alcohol-dependent patients. *Journal of Nuclear Medicine*, *61*(2), 256-262. https://doi.org/10.2967/jnumed.119.228825

Chiang, S. S., Schuetz, C. G., & Soyka, M. (2002). Effects of irritability on craving before and after cue exposure in abstinent alcoholic inpatients: experimental data on subjective response and heart rate. *Neuropsychobiology*, *46*(3), 150-160. https://doi.org/10.1159/000066392

Cho, S., Ku, J., Park, J., Han, K., Lee, H., Choi, Y. K., ... & Shen, D. F. (2008). Development and verification of an alcohol craving–induction tool using virtual reality: craving characteristics in social pressure situation. CyberPsychology *& Behavior*, *11*(3), 302-309. https://doi.org/10.1089/cpb.2007.0149

Choi, Y. J., & Lee, J. H. (2015). The effect of virtual covert sensitization on reducing alcohol craving in heavy social drinkers. *Virtual Reality*, *19*(2), 111-117. https://doi.org/10.1007/s10055-015-0264-6

Cohen, J. (1988). Set correlation and contingency tables. *Applied psychological measurement*, *12*(4), 425-434. https://doi.org/10.1177/014662168801200410

Conklin, C. A., & Tiffany, S. T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction*, *97*(2), 155-167. https://doi.org/10.1046/j.1360-0443.2002.00014.x

Cooney, N. L., Litt, M. D., Cooney, J. L., Pilkey, D. T., Steinberg, H. R., & Oncken, C. A. (2009). Alcohol and tobacco cessation in alcohol-dependent smokers: analysis of real-time reports. https://doi.org/10.1037/11855-020

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour research and therapy*, *58*,

10-23. https://doi.org/10.1016/j.brat.2014.04.006

Degenhardt, L., Glantz, M., Evans-Lacko, S., Sadikova, E., Sampson, N., Thornicroft, G., ... & Zaslavsky, A. M. (2017). Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys. *World Psychiatry*, *16*(3), 299-307. https://doi.org/10.1002/wps.20457

Doñamayor, N., Ebrahimi, C., Garbusow, M., Wedemeyer, F., Schlagenhauf, F., & Heinz, A. (2021). Instrumental and Pavlovian Mechanisms in Alcohol Use Disorder. *Current Addiction Reports*, 1-25. https://doi.org/10.1007/s40429-020-00333-9

Drobes, D. J., & Thomas, S. E. (1999). Assessing craving for alcohol. *Alcohol Research & Health*, *23*(3), 179.

Drummond, D. C. (2001). Theories of drug craving, ancient and modern. *Addiction*, *96*(1), 33-46. https://doi.org/10.1046/j.1360-0443.2001.961333.x

Drummond, D. C., & Glautier, S. (1994). A controlled trial of cue exposure treatment in alcohol dependence. *Journal of consulting and clinical psychology*, *62*(4), 809. https://doi.org/10.1037/0022-006X.62.4.809

Duka, T., Townshend, J. M., Collier, K., & Stephens, D. N. (2002). Kindling of withdrawal: a study of craving and anxiety after multiple detoxifications in alcoholic inpatients. *Alcoholism: Clinical and Experimental Research*, *26*(6), 785-795. https://doi.org/10.1111/j.1530-0277.2002.tb02606.x

Durl, J., Dietrich, T., Pang, B., Potter, L. E., & Carter, L. (2018). Utilising virtual reality in alcohol studies: A systematic review. *Health Education Journal*, *77*(2), 212-225. https://doi.org/10.1177/0017896917743534

Enkema, M. C., Hallgren, K. A., Bowen, S., Lee, C. M., & Larimer, M. E. (2021). Craving management: Exploring factors that influence momentary craving-related risk of cannabis use among young adults. *Addictive behaviors*, *115*, 106750. https://doi.org/10.1016/j.addbeh.2020.106750

Ferrer-García, M., & Gutiérrez-Maldonado, J. (2012). The use of virtual reality in the study, assessment, and treatment of body image in eating disorders and nonclinical samples: a

review of the literature. *Body image*, *9*(1), 1-11. https://doi.org/10.1016/j.bodyim.2011.10.001

Fox, J., Arena, D., & Bailenson, J. N. (2009). Virtual reality: A survival guide for the social scientist. *Journal of Media Psychology*, *21*(3), 95-113. https://doi.org/10.1027/1864-1105.21.3.95

Fox, H. C., Bergquist, K. L., Hong, K. I., & Sinha, R. (2007). Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. *Alcoholism: Clinical and Experimental Research*, *31*(3), 395-403. https://doi.org/10.1111/j.1530-0277.2006.00320.x

Gatti, E., Massari, R., Sacchelli, C., Lops, T., Gatti, R., & Riva, G. (2008). Why do you drink? Virtual reality as an experiential medium for the assessment of alcohol-dependent individuals. *Studies in health technology and informatics*, *132*, 132-137.

Ghiţă, A., & Gutiérrez-Maldonado, J. (2018). Applications of virtual reality in individuals with alcohol misuse: a systematic review. *Addictive behaviors*, *81*, 1-11. https://doi.org/10.1016/j.addbeh.2018.01.036

Ghiţă, A., Hernández-Serrano, O., Fernández-Ruiz, Y., Monras, M., Ortega, L., Mondon, S., ... Gutiérrez-Maldonado, J. (2019a). Cue-elicited anxiety and alcohol craving as indicators of the validity of ALCO-VR software: A Virtual Reality study. *Journal of clinical medicine*, *8*(8), 1153. https://doi.org/10.3390/jcm8081153

Ghiţă, A., Hernández-Serrano, O., Ruiz, J., Monras, M., Ortega, L., Mondon, S., ... Gutiérrez, J. (2019b). Craving and Anxiety Responses as Indicators of the Efficacy of Virtual Reality-Cue Exposure Therapy in Patients Diagnosed with Alcohol use Disorder. *Annual Review of Cybertherapy And Telemedicine 2019*, 77.

Ghiţă, A., Hernández-Serrano, O., Fernández-Ruiz, J., Moreno, M., Monras, M., Ortega, L., ... & Gutiérrez-Maldonado, J. (2021). Attentional Bias, Alcohol Craving, and Anxiety Implications of the Virtual Reality Cue-Exposure Therapy in Severe Alcohol Use Disorder: A Case Report. *Frontiers in Psychology*, *12*, 169. https://doi.org/10.3389/fpsyg.2021.543586

Ghiţă, A., Teixidor, L., Monras, M., Ortega, L., Mondon, S., Gual, A., ... Gutiérrez-Maldonado, J. (2019). Identifying triggers of alcohol craving to develop effective virtual environments for cue exposure therapy. *Frontiers in psychology*, *10*, 74.

https://doi.org/10.3389/fpsyg.2019.00074

Grissom, N., & Bhatnagar, S. (2009). Habituation to repeated stress: get used to it. *Neurobiology of learning and memory*, *92*(2), 215-224. https://doi.org/10.1016/j.nlm.2008.07.001

Guillamón, M. C., Solé, A. G., & Farran, J. C. (1999). Test para la identificación de transtornos por uso de alcohol (AUDIT): Traducción y validación del AUDIT al catalán y castellano. *Adicciones*, *11*(4), 337-347. https://doi.org/10.20882/adicciones.613

Haass-Koffler, C. L., Leggio, L., & Kenna, G. A. (2014). Pharmacological approaches to reducing craving in patients with alcohol use disorders. *CNS drugs*, *28*(4), 343-360. https://doi.org/10.1007/s40263-014-0149-3

Hernández-Serrano, O., Ghiţă, A., Figueras-Puigderrajols, N., Fernández-Ruiz, J., Monras, M., Ortega, L., ... & Gutiérrez-Maldonado, J. (2020). Predictors of Changes in Alcohol Craving Levels during a Virtual Reality Cue Exposure Treatment among Patients with Alcohol Use Disorder. *Journal of Clinical Medicine*, *9*(9), 3018. https://doi.org/10.3390/jcm9093018

Herrold, A. A., Pape, T. L., Li, X., & Jordan, N. (2017). Association between alcohol craving and health-related quality of life among veterans with co-occurring conditions. Military medicine, 182(7). https://doi.org/10.7205/MILMED-D-16-00360

Higgins-Biddle, J. C., & Babor, T. F. (2018). A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions. *The American journal of drug and alcohol abuse*, *44*(6), 578-586. https://doi.org/10.1080/00952990.2018.1456545

Holt, L. J., Litt, M. D., & Cooney, N. L. (2012). Prospective analysis of early lapse to drinking and smoking among individuals in concurrent alcohol and tobacco treatment. *Psychology of Addictive Behaviors, 26*(3), 561–572. https://doi.org/10.1037/a0026039

Hone-Blanchet, A., Wensing, T., & Fecteau, S. (2014). The use of virtual reality in craving assessment and cue-exposure therapy in substance use disorders. *Frontiers in human neuroscience*, *8*, 844. https://doi.org/10.3389/fnhum.2014.00844

Huang, Y., ... Kessler, R. C. (2017). Estimating treatment coverage for people with substance use

disorders: an analysis of data from the World Mental Health Surveys. *World Psychiatry, 16*, 299–307. DOI: 10.1002/wps.20457

Kavanagh, D. J., Sitharthan, G., Young, R. M., Sitharthan, T., Saunders, J. B., Shockley, N., & Giannopoulos, V. (2006). Addition of cue exposure to cognitive-behaviour therapy for alcohol misuse: a randomized trial with dysphoric drinkers. *Addiction*, *101*(8), 1106-1116. https://doi.org/10.1111/j.1360-0443.2006.01488.x

Kavanagh, D. J., Statham, D. J., Feeney, G. F., Young, R. M., May, J., Andrade, J., & Connor, J. P. (2013). Measurement of alcohol craving. *Addictive behaviors*, *38*(2), 1572-1584. https://doi.org/10.1016/j.addbeh.2012.08.004

Kaysen, D., Atkins, D. C., Simpson, T. L., Stappenbeck, C. A., Blayney, J. A., Lee, C. M., & Larimer, M. E. (2014). Proximal relationships between PTSD symptoms and drinking among female college students: Results from a daily monitoring study. *Psychology of Addictive Behaviors, 28*(1), 62–73. https://doi.org/10.1037/a0033588

Kim, D. Y., & Lee, J. H. (2015). Development of a virtual approach–avoidance task to assess alcohol cravings. *Cyberpsychology, Behavior, and Social Networking*, *18*(12), 763-766. https://doi.org/10.1089/cyber.2014.0490

Koob, G. F., Ahmed, S. H., Boutrel, B., Chen, S. A., Kenny, P. J., Markou, A., ... & Sanna, P. P. (2004). Neurobiological mechanisms in the transition from drug use to drug dependence. *Neuroscience & Biobehavioral Reviews*, *27*(8), 739-749. https://doi.org/10.1016/j.neubiorev.2003.11.007

Krahn, D. D., Bohn, M. J., Henk, H. J., Grossman, J. L., & Gosnell, B. (2005). Patterns of urges during early abstinence in alcohol-dependent subjects. *American Journal on Addictions*, *14*(3), 248-255. DOI: 10.1080/10550490590949424

Kwon, H., Choi, J., Roh, S., Yang, B. H., & Lee, J. H. (2006). Application of virtual reality-cue exposure therapy for reducing alcohol craving. *Annual Review of CyberTherapy and Telemedicine*, *4*, 161-166.

Leal, P. C., Goes, T. C., da Silva, L. C. F., & Teixeira-Silva, F. (2017). Trait vs. state anxiety in different threatening situations. *Trends in psychiatry and psychotherapy*, *39*(3), 147-157.

http://dx.doi.org/10.1590/2237-6089-2016-0044

Lebiecka, Z., Skoneczny, T., Tyburski, E., Samochowiec, J., & Kucharska-Mazur, J. (2021). Is Virtual Reality Cue Exposure a Promising Adjunctive Treatment for Alcohol Use Disorder?. *Journal of Clinical Medicine*, *10*(13), 2972. https://doi.org/10.3390/jcm10132972

Lee, J. H., Kwon, H., Choi, J., & Yang, B. H. (2007). Cue-exposure therapy to decrease alcohol craving in virtual environment. *CyberPsychology & Behavior*, *10*(5), 617-623. https://doi.org/10.1089/cpb.2007.9978

Lee, J. S., Namkoong, K., Ku, J., Cho, S., Park, J. Y., Choi, Y. K., ... & Jung, Y. C. (2008). Social pressure-induced craving in patients with alcohol dependence: application of virtual reality to coping skill training. *Psychiatry Investigation*, *5*(4), 239. DOI: 10.4306/pi.2008.5.4.239

Lee, S. H., Han, D. H., Oh, S., Lyoo, I. K., Lee, Y. S., Renshaw, P. F., & Lukas, S. E. (2009). Quantitative electroencephalographic (qEEG) correlates of craving during virtual reality therapy in alcohol-dependent patients. *Pharmacology Biochemistry and Behavior*, *91*(3), 393-397. https://doi.org/10.1016/j.pbb.2008.08.014

Litt, M. D., Cooney, N. L., & Morse, P. (2000). Reactivity to alcohol-related stimuli in the laboratory and in the field: predictors of craving in treated alcoholics. *Addiction*, *95*(6), 889-900. ttps://doi.org/10.1046/j.1360-0443.2000.9568896.x

López, V., Paladines, B., Vaca, S., Cacho, R., Fernández-Montalvo, J., & Ruisoto, P. (2019). Psychometric properties and factor structure of an Ecuadorian version of the Alcohol Use Disorders Identification Test (AUDIT) in college students. *PloS one*, *14*(7). https://doi.org/10.1371/journal.pone.0219618

Lundahl, L. H., & Johanson, C. E. (2011). Cue-induced craving for marijuana in cannabis-dependent adults. *Experimental and clinical psychopharmacology*, *19*(3), 224. https://doi.org/10.1037/a0023030

Maples-Keller, J. L., Bunnell, B. E., Kim, S. J., & Rothbaum, B. O. (2017). The use of virtual reality technology in the treatment of anxiety and other psychiatric disorders. *Harvard review of psychiatry*, *25*(3), 103. http://dx.doi.org/10.1097/HRP.0000000000000138

McCaul, M. E., Hutton, H. E., Stephens, M. A. C., Xu, X., & Wand, G. S. (2017). Anxiety, anxiety

sensitivity, and perceived stress as predictors of recent drinking, alcohol craving, and social stress response in heavy drinkers. *Alcoholism: Clinical and Experimental Research*, *41*(4), 836-845. https://doi.org/10.1111/acer.13350

Mellentin, A. I., Skøt, L., Nielsen, B., Schippers, G. M., Nielsen, A. S., Stenager, E., & Juhl, C. (2017). Cue exposure therapy for the treatment of alcohol use disorders: a meta-analytic review. *Clinical psychology review*, *57*, 195-207. https://doi.org/10.1016/j.cpr.2017.07.006

Meneses-Gaya, C. D., Zuardi, A. W., Loureiro, S. R., & Crippa, J. A. S. (2009). Alcohol Use Disorders Identification Test (AUDIT): An updated systematic review of psychometric properties. *Psychology & Neuroscience*, *2*(1), 83-97. https://doi.org/10.3922/j.psns.2009.1.12

Meneses-Gaya, C., Zuardi, A. W., Loureiro, S. R., Hallak, J. E., Trzesniak, C., de Azevedo Marques, J. M., ... & Crippa, J. A. (2010). Is the full version of the AUDIT really necessary? Study of the validity and internal construct of its abbreviated versions. *Alcoholism: Clinical and Experimental Research*, *34*(8), 1417-1424. https://doi.org/10.1111/j.1530-0277.2010.01225.x

Miranda Jr, R., O'Malley, S. S., Treloar Padovano, H., Wu, R., Falk, D. E., Ryan, M. L., ... & Litten, R. Z. (2020). Effects of alcohol cue reactivity on subsequent treatment outcomes among treatment-seeking individuals with alcohol use disorder: a multisite randomized, double-blind, placebo-controlled clinical trial of varenicline. *Alcoholism: Clinical and Experimental Research*, *44*(7), 1431-1443. https://doi.org/10.1111/acer.14352

Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., ... Asher, M. K. (2006). Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. *Alcoholism: Clinical and Experimental Research*, *25*(11), 1634-1647. https://doi.org/10.1111/j.1530-0277.2001.tb02170.x

Nadkarni, A., Garber, A., Costa, S., Wood, S., Kumar, S., MacKinnon, N., ... & Rane, A. (2019). Auditing the AUDIT: A systematic review of cut-off scores for the Alcohol Use Disorders Identification Test (AUDIT) in low-and middle-income countries. *Drug and alcohol dependence*, *202*, 123-133. https://doi.org/10.1016/j.drugalcdep.2019.04.031

NIDA (2012). Principles of drug addiction treatment: a research-based guide (third edition)

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

Papachristou, H., Nederkoorn, C., Corstjens, J., & Jansen, A. (2012). The role of impulsivity and perceived availability on cue-elicited craving for alcohol in social drinkers. *Psychopharmacology*, *224*(1), 145-153. https://doi.org/10.1007/s00213-012-2747-4

Pareaud, M., Girard, M., & Nubukpo, P. (2021). Factors for Maintaining Abstinence at 2 and 6 Months After Alcohol Withdrawal. *Journal of Psychiatric Practice®*, *27*(1), 2-13. DOI: 10.1097/PRA.0000000000000522

Paris, M. M., Carter, B. L., Traylor, A. C., Bordnick, P. S., Day, S. X., Armsworth, M. W., & Cinciripini, P. M. (2011). Cue reactivity in virtual reality: The role of context. *Addictive behaviors*, *36*(7), 696-699. https://doi.org/10.1016/j.addbeh.2011.01.029

Parsons, T. D., & Rizzo, A. A. (2008). Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: A meta-analysis. *Journal of behavior therapy and experimental psychiatry*, *39*(3), 250-261. https://doi.org/10.1016/j.jbtep.2007.07.007

Pavlov, I. P. (1927). Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex. *Ann. Neurosci. 1927, 17*(3), 136–141. DOI: 10.5214/ans.0972-7531.1017309

Reid, M. S., Mickalian, J. D., Delucchi, K. L., Hall, S. M., & Berger, S. P. (1998). An acute dose of nicotine enhances cue-induced cocaine craving. *Drug and alcohol dependence*, *49*(2), 95-104. https://doi.org/10.1016/S0376-8716(97)00144-0

Reinert, D. F., & Allen, J. P. (2007). The alcohol use disorders identification test: an update of research findings. *Alcoholism: Clinical and Experimental Research*, *31*(2), 185-199. https://doi.org/10.1111/j.1530-0277.2006.00295.x

Pericot-Valverde, I., García-Rodríguez, O., Gutiérrez-Maldonado, J., & Secades-Villa, R. (2015). Individual variables related to craving reduction in cue exposure treatment. *Addictive behaviors*, *49*, 59-63. https://doi.org/10.1016/j.addbeh.2015.05.013

Riva, G., Castelnuovo, G., & Mantovani, F. (2006). Transformation of flow in rehabilitation: the role of advanced communication technologies. *Behavior research methods*, *38*(2), 237-244. https://doi.org/10.3758/BF03192775

Riva, G., & Gaggioli, A. (2009). Rehabilitation as empowerment: The role of advanced technologies. *Studies in health technology and informatics*, *145*, 3-22.

Rothbaum, B. O., Price, M., Jovanovic, T., Norrholm, S. D., Gerardi, M., Dunlop, B., ... & Ressler, K. J. (2014). A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. *American Journal of Psychiatry*, *171*(6), 640-648. https://doi.org/10.1176/appi.ajp.2014.13121625

Ryan, J. J., Kreiner, D. S., Chapman, M. D., & Stark-Wroblewski, K. (2010). Virtual reality cues for binge drinking in college students. *CyberPsychology, Behavior, and Social Networking*, *13*(2), 159-162. https://doi.org/10.1089/cyber.2009.0211

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*, *88*(6), 791-804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Segawa, T., Baudry, T., Bourla, A., Blanc, J. V., Peretti, C. S., Mouchabac, S., & Ferreri, F. (2020). Virtual reality (VR) in assessment and treatment of addictive disorders: A systematic review. *Frontiers in neuroscience*, *13*, 1409. https://doi.org/10.3389/fnins.2019.01409

Serre, F., Fatseas, M., Swendsen, J., & Auriacombe, M. (2015). Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. *Drug and alcohol dependence*, *148*, 1-20. https://doi.org/10.1016/j.drugalcdep.2014.12.024

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., & Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol-dependent individuals. *Neuropsychopharmacology*, *34*(5), 1198-1208. https://doi.org/10.1038/npp.2008.78

Spagnoli, G., Gatti, E., Massari, R., Sacchelli, C., & Riva, G. (2014). Can virtual reality be useful to assess subjects with alcohol dependency? Development of a new assessment protocol for patients with alcoholism. *Eur. Int. J. Sci. Technol*, *3*, 82-94.

Stamou, V., Chatzoudi, T., Stamou, L., Romo, L., & Graziani, P. (2016). Music-assisted systematic

desensitization for the reduction of craving in response to drug-conditioned cues: A pilot study. *The Arts in Psychotherapy*, *51*, 36-45. https://doi.org/10.1016/j.aip.2016.08.003

Stasiewicz, P. R., Brandon, T. H., & Bradizza, C. M. (2007). Effects of extinction context and retrieval cues on renewal of alcohol-cue reactivity among alcohol-dependent outpatients. *Psychology of Addictive Behaviors*, *21*(2), 244. https://doi.org/10.1037/0893-164X.21.2.244

Stohs, M. E., Schneekloth, T. D., Geske, J. R., Biernacka, J. M., & Karpyak, V. M. (2019). Alcohol craving predicts relapse after residential addiction treatment. *Alcohol and Alcoholism*, *54*(2), 167-172. https://doi.org/10.1093/alcalc/agy093

Sung, Y. T., & Wu, J. S. (2018). The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): a new technique for psychological measurement. *Behavior research methods*, *50*(4), 1694-1715. https://doi.org/10.3758/s13428-018-1041-8

Suzuki, S., Mell, M. M., O'Malley, S. S., Krystal, J. H., Anticevic, A., & Kober, H. (2020). Regulation of craving and negative emotion in alcohol use disorder. *Biological psychiatry: cognitive neuroscience and neuroimaging*, *5*(2), 239-250. https://doi.org/10.1016/j.bpsc.2019.10.005

Szegedi, A., Lörch, B., Scheurich, A., Ruppe, A., Hautzinger, M., & Wetzel, H. (2000). Cue exposure in alcohol-dependent patients: preliminary evidence for different types of cue reactivity. *Journal of Neural Transmission*, *107*(6), 721-730. https://doi.org/10.1007/s007020070073

Trahan, M. H., Maynard, B. R., Smith, K. S., Farina, A. S., & Khoo, Y. M. (2019). Virtual reality exposure therapy on alcohol and nicotine: A systematic review. *Research on Social Work Practice*, *29*(8), 876-891. https://doi.org/10.1177/1049731518823073

Tsamitros, N., Sebold, M., Gutwinski, S., & Beck, A. (2021). Virtual Reality-Based Treatment Approaches in the Field of Substance Use Disorders. *Current Addiction Reports*, 1-9. https://doi.org/10.1007/s40429-021-00377-5

Vollstädt-Klein, S., Loeber, S., Kirsch, M., Bach, P., Richter, A., Bühler, M., ... & Kiefer, F. (2011).

Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. *Biological psychiatry*, *69*(11), 1060-1066. https://doi.org/10.1016/j.biopsych.2010.12.016

Wall, A. M., Hinson, R. E., McKee, S. A., & Goldstein, A. (2001). Examining alcohol outcome expectancies in laboratory and naturalistic bar settings: A within-subject experimental analysis. *Psychology of Addictive Behaviors*, *15*(3), 219. https://doi.org/10.1037/0893-164X.15.3.219

Wapp, M., Burren, Y., Znoj, H., & Moggi, F. (2015). Association of alcohol craving and proximal outcomes of a residential treatment program for patients with alcohol use disorders. *Journal of Substance Use*, *20*(1), 11-15.

Weech, S., Kenny, S., & Barnett-Cowan, M. (2019). Presence and cybersickness in virtual reality are negatively related: a review. *Frontiers in psychology*, *10*, 158. https://doi.org/10.3389/fpsyg.2019.00158

Williams, V. S., Morlock, R. J., & Feltner, D. (2010). Psychometric evaluation of a visual analog scale for the assessment of anxiety. *Health and quality of life outcomes*, *8*(1), 1-8. https://doi.org/10.1186/1477-7525-8-57

Wolitzky-Taylor, K., Niles, A. N., Ries, R., Krull, J. L., Rawson, R., Roy-Byrne, P., & Craske, M. (2018). Who needs more than standard care? Treatment moderators in a randomized clinical trial comparing addiction treatment alone to addiction treatment plus anxiety disorder treatment for comorbid anxiety and substance use disorders. *Behaviour research and therapy*, *107*, 1-9. https://doi.org/10.1016/j.brat.2018.05.005

Zironi, I., Burattini, C., Aicardi, G., & Janak, P. H. (2006). Context is a trigger for relapse to alcohol. Behavioural Brain Research, 167(1), 150–155. http://dx.doi.org/10.1016/j.bbr.2005.09.007

Appendix A

Spanish version of the AUDIT

AUDIT

PACIENTE: Debido a que el uso del alcohol puede afectar su salud e interferir con ciertos medicamentos y tratamientos, es importante que le hagamos algunas preguntas sobre su uso del alcohol. Sus respuestas serán confidenciales, así que le agradecemos su honestidad.

Para cada pregunta en la tabla siguiente, marque una X en el cuadro que mejor describa su respuesta.

NOTA: En los Estados Unidos *una bebida* se refiere a cualquier bebida que contiene aproximadamente 14 gramos de etanol o alcohol puro. Las bebidas que siguen a continuación son de diferentes tamaños sin embargo su contenido de alcohol es el mismo. Es por eso que todas son consideradas *una bebida*:

Preguntas	0	1	2	3	4	
1. ¿Con qué frecuencia consume alguna bebida alcohólica?	Nunca	Una o menos veces al mes	De 2 a 4 veces al mes	De 2 a 3 más veces a la semana	4 o más veces a la semana	
2. ¿Cuantas consumiciones de bebidas alcohólicas suele realizar en un día de consumo normal?	1 o 2	3 o 4	5 o 6	De 7 a 9	10 o más	
3. ¿Con qué frecuencia toma 5 o más bebidas alcohólicas en un solo día?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
4. ¿Con qué frecuencia en el curso del último año ha sido incapaz de parar de beber una vez había empezado?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
5. ¿Con qué frecuencia en el curso del último año no pudo hacer lo que se esperaba de usted porque había bebido?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
6. ¿Con qué frecuencia en el curso del último año ha necesitado beber en ayunas para recuperarse después de haber bebido mucho el día anterior?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
7. ¿Con qué frecuencia en el curso del último año ha tenido remordimientos o sentimientos de culpa después de haber bebido?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
8. ¿Con qué frecuencia en el curso del último año no ha podido recordar lo que sucedió la noche anterior porque había estado bebiendo?	Nunca	Menos de una vez al mes	Mensualmente	Semanalmente	A diario o casi a diario	
9. ¿Usted o alguna otra persona ha resultado herido porque usted había bebido?	No		Sí, pero no en el curso del último año		Sí, el último año	
10. ¿Algún familiar, amigo, médico o profesional sanitario ha mostrado preocupación por un consumo de bebidas alcohólicas o le ha sugerido que deje de beber?	No		Sí, pero no en el curso del último año		Sí, el último año	
					Total	

Nota: Este cuestionario (el AUDIT) se reimprime con permiso de la Organización Mundial de la Salud y la Generalitat Valenciana Conselleria de Benestar Social. Para reflejar las medidas de consumo en los Estados Unidos (14 gramos de alcohol puro), la cantidad de tragos en la pregunta 3 fue cambiada de 6 a 5. En el sitio *www.who.org* está disponible en forma gratuita un manual AUDIT con guías para su uso en la atención primaria.

Excerpted from NIH Publication No. 07-3769 **National Institute on Alcohol and Alcoholism** *www.niaaa.nih.gov/guide*

Appendix B

QQ-plots for normality testing

Figure 3

Normal Q-Q Plots of AUDIT

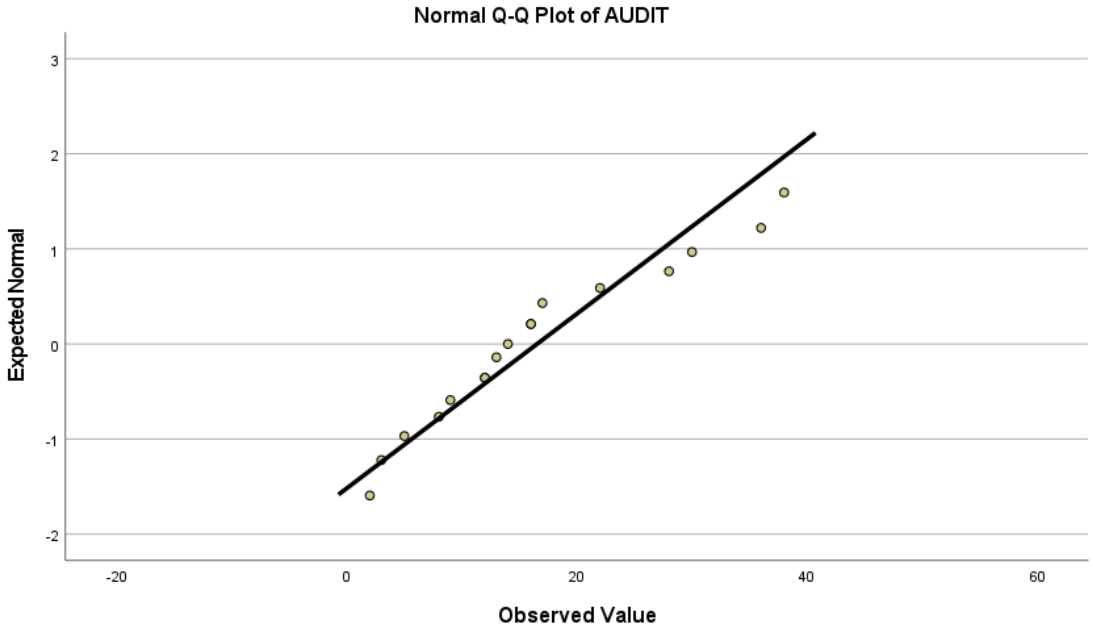


Figure 4

Q-Q plots of VAS-A neutral VR-environment at baseline

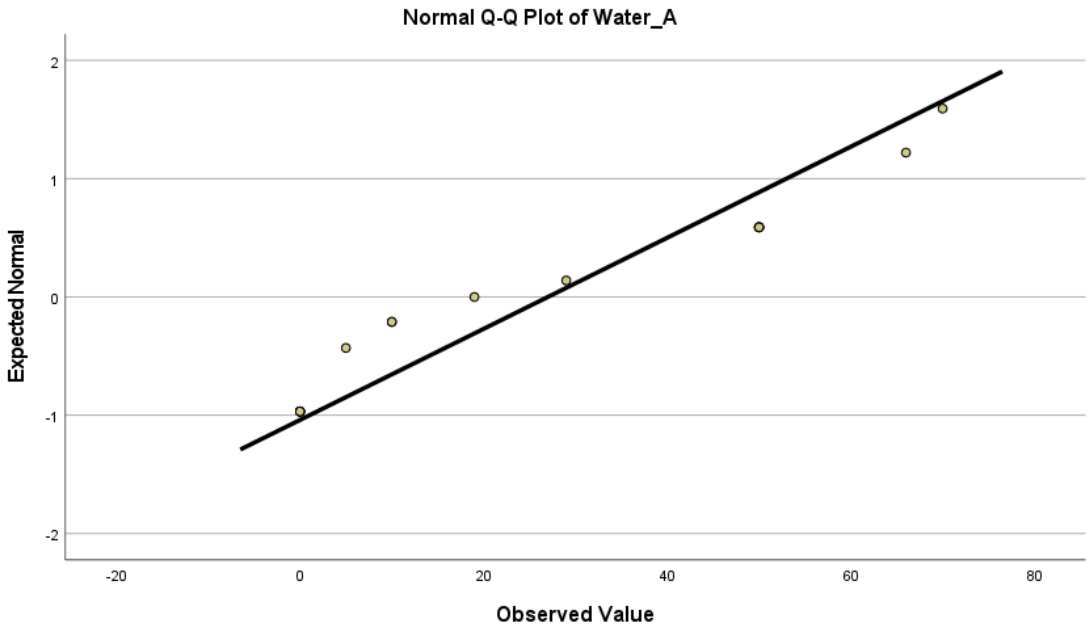


Figure 5

Q-Q plots of VAS-C neutral VR-environment at baseline

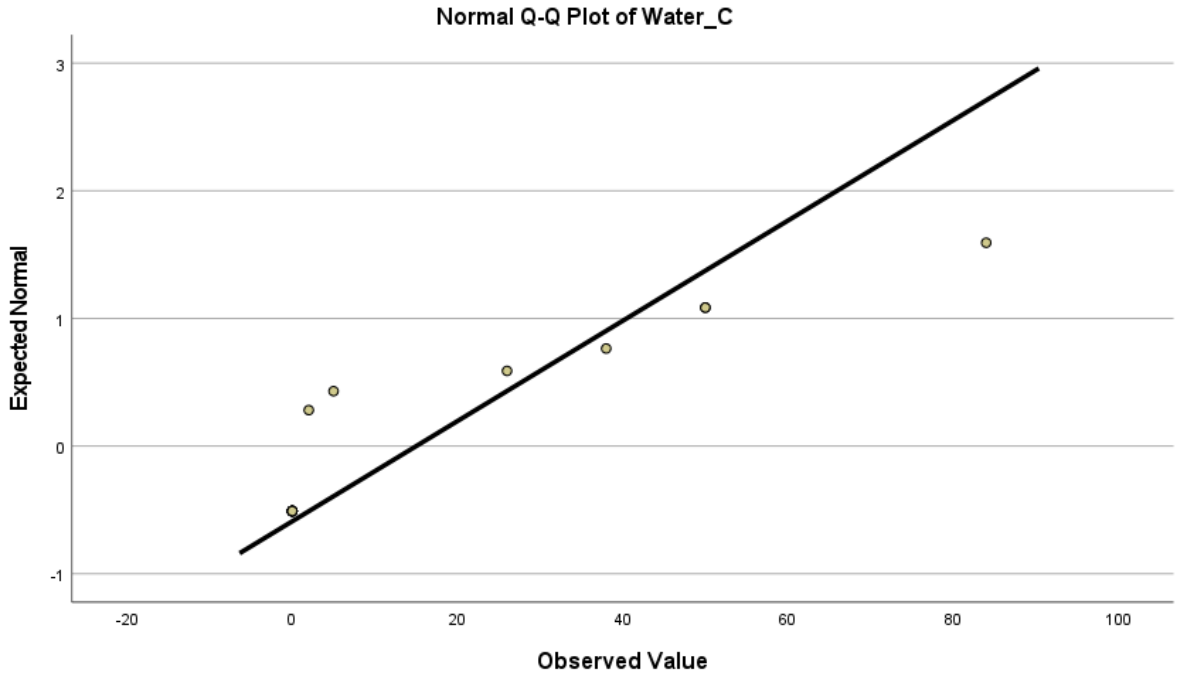


Figure 6

Q-Q plots of VAS-C alcohol-related environments at baseline (T0)

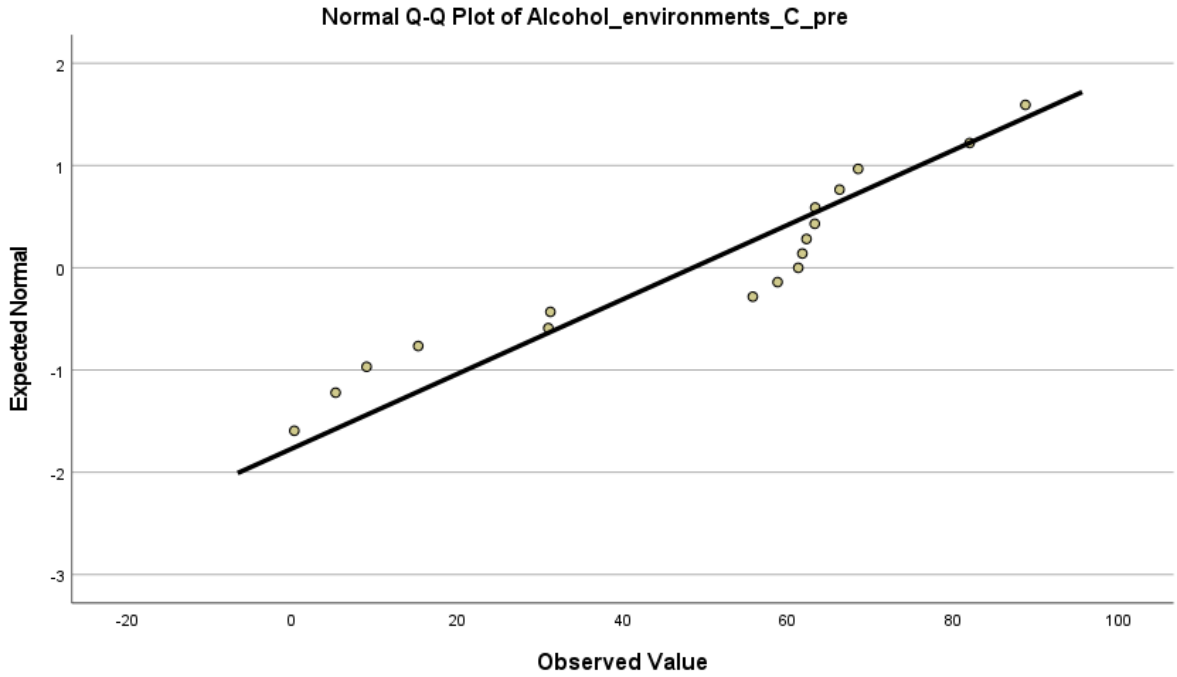


Figure 7

Q-Q plots of VAS-C alcohol-related environments at final assessment (T1)

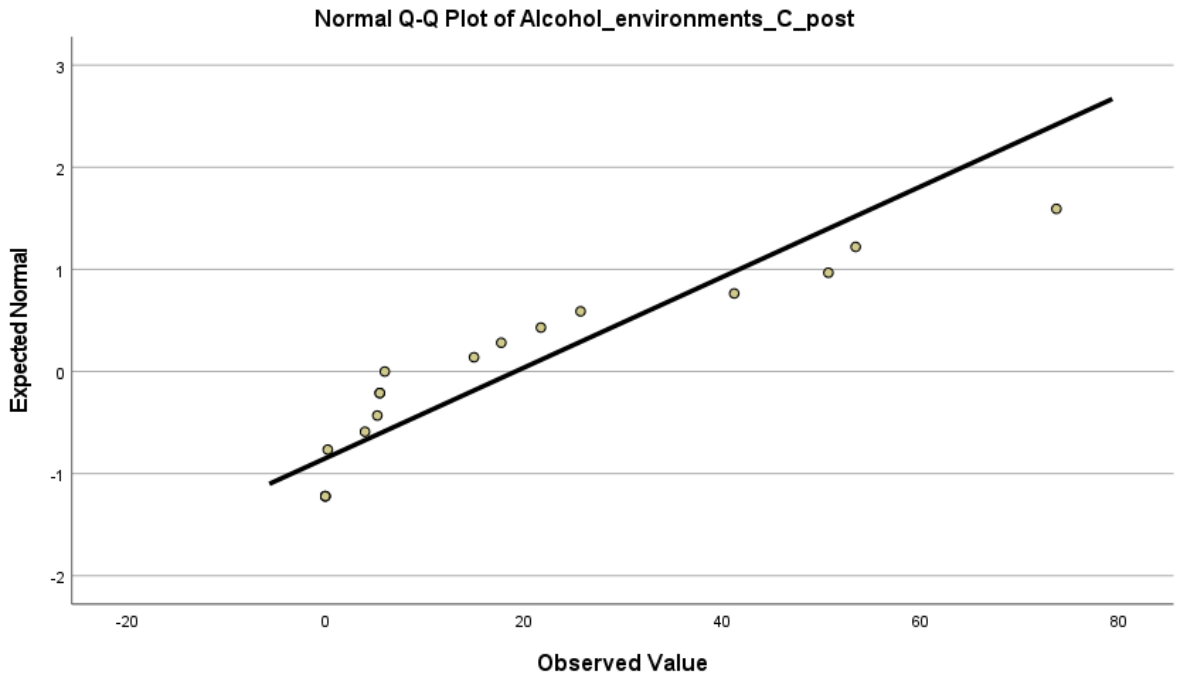


Figure 8

Q-Q plots VAS-A alcohol-related environments at baseline (T0)

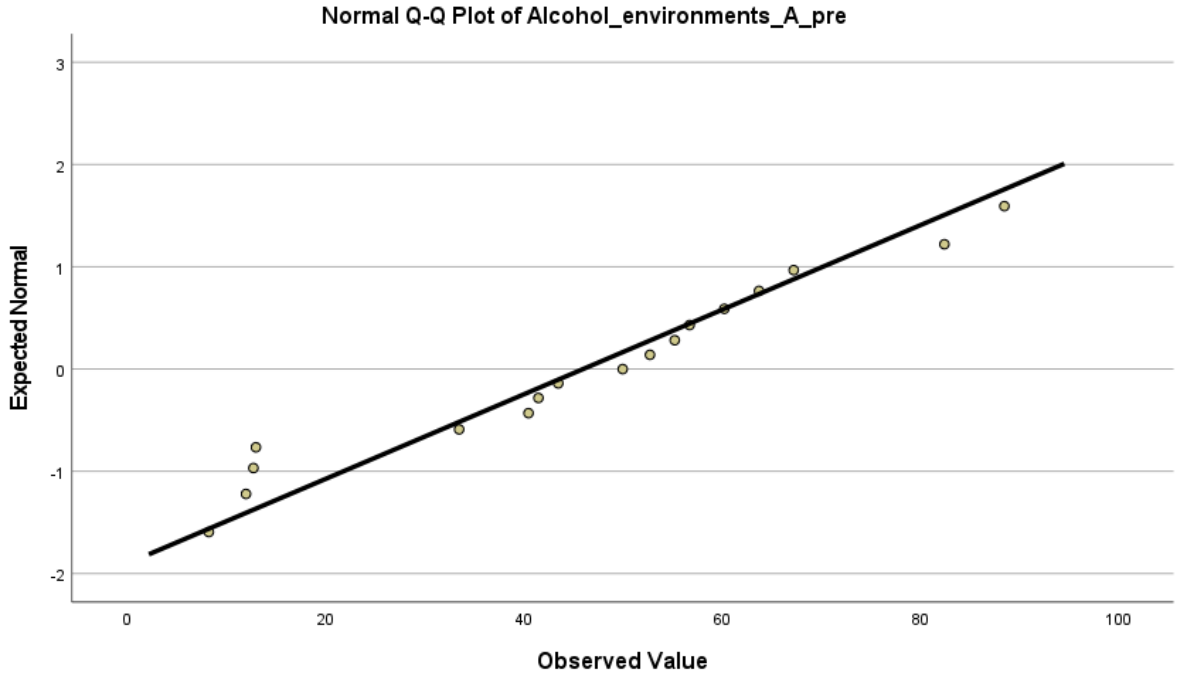
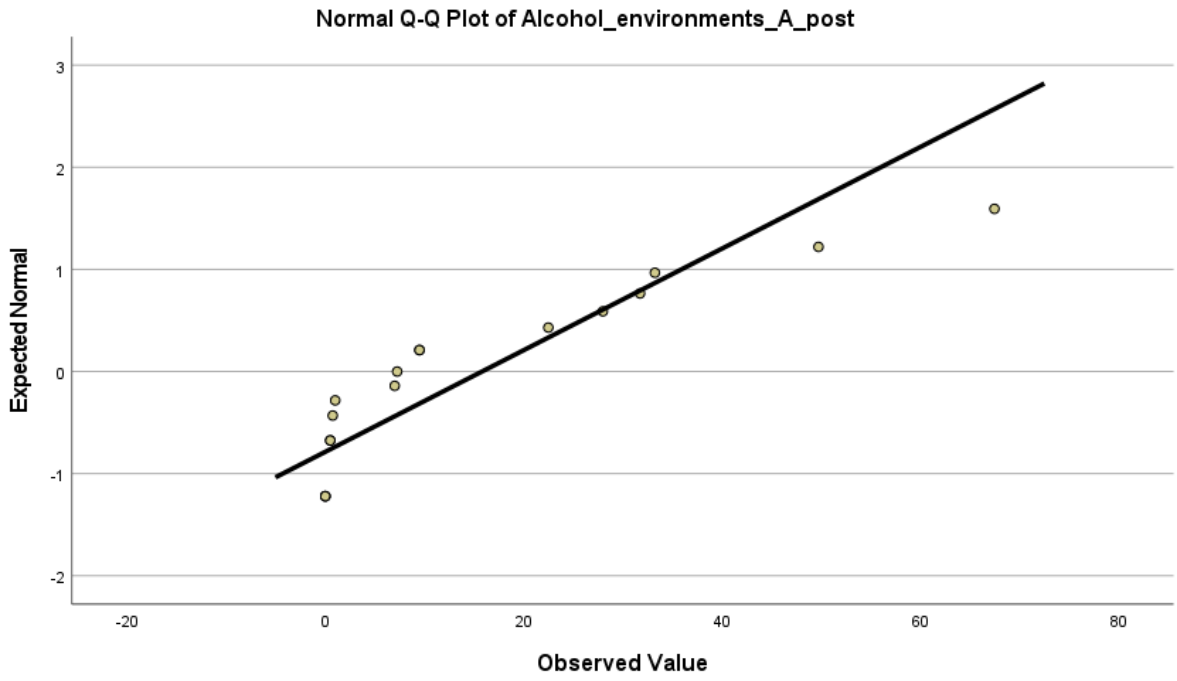


Figure 9

Q-Q plots VAS-A alcohol-related environments at final assessment (T1)


Normal Q-Q Plot of Alcohol_environments_A_post
Expected Normal
Observed Value
3
2
1
0
-1
-2
-20
0
20
40
60
80