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The relationship between perceived stress and cue sensitivity for alcohol

MICHELLE SNELLEMAN^{A,B,*}, TIM M. SCHOENMAKERS^{A,B}, DIKE VAN DE MHEEN^{A,B,C}

a IVO Addiction Research Institute, Heemraadssingel 194, 3021 DM, Rotterdam, The Netherlands

b Erasmus Medical Center Rotterdam, P.O. box 2040, 3000 CA, Rotterdam, The Netherlands

c Department of Health Promotion, Maastricht University, P.O. box 616, 6200 MD Maastricht, The Netherlands

ABSTRACT

Previous research has shown that cue sensitivity and stress affect the risk for relapse in alcohol-dependent patients. Theoretically, a link between the two can be expected. However, a clear overview of the interplay of these factors is not yet available. The purpose of this review was to examine the empirical evidence for the influence of stress on sensitivity for alcohol-related cues.

Empirical studies indexed in PubMed, EMBASE, PsycINFO, and Web of Knowledge that assessed the relation between stress and sensitivity for alcohol-related cues using subjective, behavioral and/or physiological measures were included in the review.

Of the 359 articles screened, 12 were included in the review. Nine articles supported the existence of the relationship between stress and heightened cue sensitivity for alcohol-related cues, whereas three articles did not support our hypothesis.

We conclude that the relationship between stress and sensitivity to alcohol cues appears to exist. In fact, there may be different factors at play: our review points toward (1) differences between the effect of psychological stress and physiological stress on cue-sensitivity, and (2) individual differences regarding coping drinking which may explain stress-induced cues sensitivity.

1. INTRODUCTION

Despite years of research and great progress in developing treatments for alcohol dependence, rates of alcohol relapse remain high (Boothby and Doering, 2005 and Finney et al., 1996). A number of theories regarding the reasons for relapse focus on the role of stress and sensitivity for alcohol-related cues or ‘stimuli.’ For example, according to the Affective Processing Model of Negative Reinforcement (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004), stressors cause or increase

negative affect, which in turn activates the learned rewarding properties of alcohol (or other addictive substances) that relieve negative affect, thereby motivating the individual to use again.

Another factor contributing to increased risks of relapse is cue sensitivity. Hereby we mean that the brain is sensitive to alcohol-related cues, leading to a strong reaction toward these cues, i.e., cue reactivity. According to the Incentive Sensitization Theory (Robinson & Berridge, 1993), specific cues (e.g., stimuli, situations) become associated with an addictive substance through repetitive use in the presence of these cues. The substance-related cues become attractive and therefore salient to the addict and activate a neurological hypersensitive reaction to a substance (Grüsser et al., 2004 and Tapert et al., 2003). This hypersensitivity may remain even after long periods of abstinence (Robinson & Berridge, 2001, cf. Koob & Le Moal, 2001). Combining the two aforementioned theories, we hypothesized that under stress, cues that have become associated with alcohol via previous experience become more salient, and the brain is more sensitive to these cues.

In experimental studies, stress has been induced by various types of stressors. Dickerson and Kemeny (2004) categorized acute psychological stressors into five types of stress induction procedures: performance of cognitive tasks; public speaking with verbal interaction; a combination of the aforementioned; noise exposure; and real (e.g., pictures, film) or mental (i.e., imagination, recall) exposure to emotion-eliciting material or situations. All five types of stress induction evoke psychological distress, and public speaking combined with a cognitive task also evokes physiological stress.

There are a number of methods to assess cue sensitivity: physiological measures, subjective measures, behavioral measures, or a combination of these measures. Physiological measures that are most often used include heart rate or heart rate variability (HRV) and skin conductance (Carter and Tiffany, 1999, Cooney et al., 1997 and Waters et al., 2009).

Cue sensitivity may also be measured subjectively and is often defined as increases in craving or the desire for alcohol after encountering alcohol-related cues (e.g., Bohn et al., 1995 and Schulze and Jones, 2000). Finally, another indicator of cue sensitivity is attentional bias, i.e. a selective focus on alcohol-related cues.

Attentional bias is assessed with a reaction time task assessing the extent to which alcohol-related cues are selectively attended to as compared to neutral cues (Field & Cox, 2008).

2. METHODS

A literature search was conducted using PubMed, EMBase/Medline, Web of Knowledge, and PsycINFO, covering all articles published until September 2013. We used the following key terms: alcohol* and ethanol*; cue*, trigger*, stimuli; stress*, ACTH, CRF, cortisol, HPA, and distress; reactivity, sensitivity, cognitive bias and implicit cognition. A total of 12 articles were selected (Fig. 1).

[FIGURE 1]

3. RESULTS

The number of identified eligible studies for this review was relatively small and study samples were diverse. Therefore, we opted for a descriptive synthesis of the

results including a calculation of effect sizes. Characteristics of the 12 included articles are presented in Table 1.

[TABLE 1]

We found three global categories of studies based on their design. Studies in category one used experimental within-subjects designs. These designs are the best test of causal relationships and therefore provide the strongest evidence. The second strongest category includes experimental studies using between-subjects designs. These studies are considered to provide somewhat weaker evidence than category one, because participants are exposed to only one mood induction condition. The third category with the weakest evidence includes correlational studies from which no causal inferences can be made.

3.1. Category 1

In the first category ($N = 5$), participants were exposed to both a stress and a neutral mood induction. Stress was induced by either using imagery (exposure to emotion-eliciting material) or performing a high-speed task (cognitive task). Cues were presented in vivo by the sight and/or smell of the preferred beverage (Coffey et al., 2006, Jansma et al., 2000, Nosen et al., 2012, Pratt and Davidson, 2009 and Ray, 2011).

Coffey et al. (2006) found that participants reported greater craving after trauma imagery followed by an alcohol cue than after trauma imagery followed by a water cue, or after neutral imagery followed by either an alcohol cue or a water cue. These results indicate that trauma-induced stress and exposure to alcohol cues increases craving as compared to neutral mood states and alcohol cues.

Similar results were obtained in another study (Nosen et al., 2012). The greatest increases in craving and salivary flow were observed after trauma imagery was followed by an alcohol cue and these increases were larger than after neutral mood induction and alcohol cue exposure. Both studies support our hypothesis.

Jansma et al. (2000) found that in all conditions (mood induction: distressed, depressed, and neutral), heart rate was lower, and heart rate variability, blood pressure and self-reported desire to drink were higher during alcohol cue exposure than during each mood induction; this hints toward an overall alcohol cue sensitivity.¹ However, there were no differences in alcohol cue sensitivity measures between conditions. Therefore, this study does not support our hypothesis: the changes induced by exposure to alcohol-related cues were not affected by negative or distressed moods.

In a study conducted by Ray (2011), the results showed that in both mood groups, alcohol cues increased the urge to consume alcohol. In contrast to our hypothesis, alcohol cues produced greater increases in the urge to drink in the neutral mood condition than in the stressed mood condition.

Finally, in the study by Pratt and Davidson (2009), there were no significant differences in craving between the stress and neutral mood condition. This indicates that stress did not lead to increased cue sensitivity, in contrast to our hypothesis.

However, the authors of the study suggested that this finding may have been caused by a ceiling effect, since craving rates in all conditions were relatively high.

Alternatively, craving was measured after alcohol consumption, which we believe may have had an attenuating effect on craving.

In sum, two studies in category one provided evidence that supported our hypothesis that stress affects cue sensitivity (Coffey et al., 2006 and Nosen et al., 2012), whereas the remaining three studies did not (Jansma et al., 2000, Pratt and Davidson, 2009 and Ray, 2011).

3.2. Category 2

All studies in the second category ($N = 3$) used stressful tasks (i.e., giving an oral presentation that would be evaluated, a public speaking task with verbal interaction) to induce stress in addition to either in vivo presentation of alcohol-related cues including physiological and subjective measurements of cue sensitivity (Nesic & Duka, 2006), or an attentional bias task that exposed participants to alcohol-related pictures (Field and Powell, 2007 and Field and Quigley, 2009).

Two separate studies were almost identical in the type of sample selected, study design and recorded measures. In both studies, an attentional bias for alcohol-related pictures was observed only after exposure to the stressor, but not after neutral mood induction. However, this effect was found only in the group of heavy social drinkers whose primary drinking motive was 'drinking to cope'. Thus, these studies support our hypothesis, but only in a subset of drinkers.

In the third study (Nesic & Duka, 2006) both groups exhibited increased skin conductance during cue exposure and increases in craving after cue exposure, indicating overall cue sensitivity. However, no differences were found in craving between the stress and neutral condition. Effects of stress on skin conductance differed between male and female participants: in males, no differences were found between the stress and the neutral condition, whereas in females, skin conductance increased during alcohol cue exposure only in the neutral condition. Thus, this study did not support our hypothesis.

Of the three studies of this category, all of which included heavy social drinkers, two supported our hypothesis. The two supporting studies (Field and Powell, 2007 and Field and Quigley, 2009) however, reported effects in coping drinkers only.

3.3. Category 3

In the correlational studies of the third category ($N = 2$, reported in four articles), all participants were exposed to a stress induction, but there was no neutral mood induction. Stress was induced by looking at aversive pictures (exposure to emotion-eliciting material) and cues consisted of alcohol-related pictures. Cue sensitivity was assessed by measuring changes between subjective pre-stress induction and post-cue exposure craving (Garland, 2011, Garland, Carter, Ropes and Howard, 2012 and Garland, Franken, Sheetz and Howard, 2012) or using an attentional bias task (Garland et al., 2010).

In the first study, which was cited in three articles (Garland, 2011, Garland, Carter, Ropes and Howard, 2012 and Garland, Franken, Sheetz and Howard, 2012), the results demonstrated an increase in self-reported stress from pre-stress induction (i.e. before stress induction and cue exposure) to post-exposure (i.e. after cue exposure) and a simultaneous increase in craving. Both stress and craving were measured before stress induction and after cue exposure but not in between. Therefore, these results provide correlational evidence supporting our hypothesis: there is evidence that increased stress is associated with increases in craving after cue exposure in alcohol-dependent patients.

The second study (Garland et al., 2010) was selected because of an embedded stress induction and cue exposure paradigm. The paradigm was used before and after treatment (10-week interval). In this study, reduced levels of stress after mindfulness training co-occurred with reduced attentional bias. This study indicates that stress levels may affect sensitivity to alcohol-related cues.

Three of the four articles describe the results of a single study (Garland, 2011, Garland, Carter, Ropes and Howard, 2012 and Garland, Franken, Sheetz and Howard, 2012) and all articles in this category provide correlational evidence supporting our hypothesis. Because of the nature of correlational designs, we cannot draw conclusions about the causal relationship between stress and cue sensitivity. We can infer, however, that changes in stress levels and cue sensitivity measures are associated.

4. DISCUSSION

In the present review, we examined evidence supporting the relationship between stress and cue sensitivity. Overall, we conclude that the relationship between stress and cue sensitivity seems to exist; however, it is complex. Mixed results were reported in the review studies. We observed that stress increased cue reactivity in 6 of 10 studies (reported in 12 articles). Our hypothesis was supported mostly by experimental between-subjects studies (category 2; $N = 2$) and correlational studies (category 3; $N = 4$) with medium to large effect sizes. However, it should be noted that these designs are considered to be weaker than experimental within-subjects studies (category 1) in their ability to infer causal relationships. Of the studies using within-subjects designs, three did not support our hypothesis whereas two (one of medium effect size, one large) did support it. It is noteworthy that the two supporting studies from category 1 sampled patients with comorbid PTSD and that the two supporting studies from category 2 found effects in coping drinkers only. Thus the four experimental studies that supported our hypothesis all studied specific groups of participants.

Considering the positive findings reported by within-subjects and between-subjects studies, it appears that stress-induced cue sensitivity exists in coping drinkers and alcohol-dependent patients with PTSD. Individuals of the latter group are likely to comprise mostly coping drinkers as well. Often, people with PTSD may become dependent on alcohol because of its rewarding properties to reduce stress and negative affect (Dixon et al., 2009, Stewart et al., 2004 and Ullman et al., 2006). Thus, these people can be viewed as drinking to cope with negative affect. Therefore coping drinking seems to be a moderating factor in the relationship between stress and cue sensitivity.

Using the present review as a basis, it appears that stress induced via exposure to emotion-eliciting material, i.e., psychological stress, led to increased cue sensitivity, while stress induced via cognitive tasks, i.e., physical and psychological stress did not. This finding may be explained in light of the Affective Processing Model of Negative Reinforcement (Baker et al., 2004) as referred to in the introduction.

Exposure to emotion-eliciting material evokes more negative affect as compared to cognitive induction tasks, the latter evoking more physical stress and arousal.

Therefore, it could be that the exposure to emotion-eliciting material evokes negative affective states comparable to those that were alleviated by drinking in the past (i.e. drinking to cope; Cooper, 1994). As a conditioned effect, when confronted with this

type of affect one is motivated to alleviate this by drinking, which enhances the rewarding properties of alcohol cues and thus cue sensitivity.

On the other hand, cognitive tasks evoke more physical stress and an acute arousal state. These states may be evoked less often in daily life. Furthermore, because of their more transient nature they have less likely been alleviated by drinking as a coping mechanism. Therefore, we believe that the conditioned effect that occurs in coping drinkers after psychological stress is unlikely to occur to the same extent after acute physical stress. In general, these acute stress states thus have no significant link with past drinking and therefore do not enhance cue sensitivity.

In future research, the type of stress of interest should be considered. Based on the above, we would suggest that evoking negative states that have been paired with drinking in the past is more important in alcohol cue sensitivity than acute arousal states that are less frequent in daily life and were not often accompanied by drinking. To examine the effect of physical and psychological stress on cue sensitivity, three types of measures should then be incorporated: self-report measures, physiological measures and attentional bias measures. In this review, we reviewed studies using one or two of these types of measures, but not a single study used all three types of measures. In addition, the role of coping drinking should be examined in detail, to investigate whether coping drinking plays a role in the relationship between stress and cue sensitivity.

Since there are not many studies yet with a strong study design, there is a clear need for replication, rendering our conclusions tentative. There may be different factors at play. Our review points toward (1) differences between the effect of psychological stress and physiological stress on cue-sensitivity, and (2) individual differences regarding coping drinking which may explain stress-induced cues sensitivity. We conclude that the relationship between stress and sensitivity to alcohol cues appears to exist, most noticeably in people who drink to cope with negative affect.

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Contributors

Prof. dr. van de Mheen reviewed and commented the protocol and the manuscript. Dr. Schoenmakers has written the protocol, assisted with the literature selection, and reviewed the manuscript. Ms. Snelleman carried out the literature search and selection, analyzed the data and has written the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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TABLES AND FIGURES

Fig. 1. Search strategy and selection process of articles in review.

Table 1
Summary of selected articles for the effect of stress on cue sensitivity.

Study	Sample	Type of mood induction	Type of cue exposure	Study design	Results on effect of stress on cue sensitivity
Coffey, Stasiewicz, Hughes, and Brimo (2006)	43 outpatients with comorbid AD and PTSD	Personalized trauma imagery script vs. neutral script	Sight and smell of participant's preferred alcoholic beverage vs. bottled spring water	Within-subject design. CS measures: craving	Craving increased when confronted with trauma and alcohol cues compared to neutral mood and alcohol cue combination (Cohen's $d = 0.86$)
Field and Powell (2007)	44 heavy social drinking students (19 low CM, 25 high CM)	Expectation of giving a speech and being evaluated vs. solving simple anagrams	Alcohol-related vs. neutral pictures during a visual probe task	Between-subject design. CS measure: attentional bias for alcohol-related pictures	in high CM drinkers only, stress induction led to an increase in attentional bias for alcohol-related cues (Cohen's $d = 1.40$), as compared to neutral mood induction (Cohen's $d = 0.18$)
Field and Quigley (2009)	58 heavy social drinking students (28 low CM; 30 high CM)	Expectation of giving a speech and being evaluated vs. solving simple anagrams	Alcohol-related vs. neutral pictures during a visual probe task	Between-subject design. CS measure: attentional bias for alcohol-related pictures	In high CM drinkers only, stress induction led to an increase in attentional bias for alcohol-related cues as compared to neutral mood induction for both attentional engagement (Cohen's $d = 1.39$) and attentional maintenance (Cohen's $d = 0.64$)
Garland (2011), Garland, Carter, Ropes, and Howard (2012), Garland, Franken, Sheetz, and Howard (2012)	58 abstinent alcohol-dependent patients, in treatment	Looking at aversive pictures	Looking at alcohol-related pictures	Correlational design. CS measure: change in craving pre- to posttest	There was a significant correlation between change in stress and change in craving, when comparing baseline and post-alcohol cue exposure (Pearson's $r = 0.57$)
Garland, Gayford, Boettiger, and Howard (2010)	53 abstinent alcohol-dependent patients in treatment	Looking at aversive pictures	Looking at alcohol-related pictures	Between-subject design, with correlational outcome. Mindfulness therapy vs. standard support group therapy (random allocation), CS measure: dot-probe task both pre and post treatment	A reduction of stress after 10 weeks of mindfulness (Cohen's $d = 0.74$) accompanied a reduced attentional bias for alcohol-related cues (Cohen's $d = 1.03$).
Jansma, Breteleur, Schippers, De Jong, and Van Der Staak (2000)	40 abstinent inpatient alcoholics	All participants: neutral mood induction: reading a family magazine. Half of participants distressed induction: performing a high speed complicated task while receiving negative feedback. Other half: depressing mood by listening to depressing mood with the instruction to get sad	Pouring a glass from a bottle of alcohol and sniff the glass five consecutive times. No neutral cue	Combined within and between-subject design. CS measures: desire to drink, blood pressure, and heart rate variability	Alcohol cue sensitivity was found, but not dependent on mood. Cue sensitivity was not higher when distressed or depressed as compared to a neutral mood for all measures: Desire to drink: Cohen's $d = 0.15$ Heart rate variability: Cohen's $d = 0.00$ Blood pressure: Cohen's $d = 0.11$
Nesic and Duka (2006)	32 heavy social drinking students	Prepare and deliver a 5-min speech followed by a mental arithmetic task. Control condition: looking at an art history book, assessing paintings and completing dot-to-dot pictures	Holding and smelling the participant's preferred alcoholic beverage	Between-subjects design. CS measures: skin conductance and desire for alcohol, measured after stress manipulation and after alcohol cue exposure	Overall effects of cue exposure were found for mild desire (Cohen's $d = 1.16$) and strong desire (Cohen's $d = 1.28$), however, there was no difference in desire for alcohol after cue exposure between the stress and control condition (Cohen's $d = 0.39$). Skin conductance increased in non-stressed females (Cohen's $d = 2.01$), but not in stressed males (Cohen's $d = 0.37$), and females (Cohen's $d = 0.73$), and in non-stressed males (Cohen's $d = 1.97$)
Nosen et al. (2012)	108 treatment-seeking adults with comorbid PTSD and alcohol dependence	Trauma imagery (narrative description of person's worst traumatic event) vs. neutral imagery (narrative about changing a light bulb)	Alcohol cue was the participant's preferred beverage. Neutral cue was a bottle of water	Within-subjects design. CS measures: positive and negative affect, and alcohol craving. All participants underwent four counterbalanced imagery-cue combinations: neutral-neutral (NN), trauma-neutral (TN), neutral-alcohol (NA) and trauma-alcohol (TA)	There was a significant difference in alcohol craving after trauma imagery followed by alcohol cues as compared to neutral mood followed by alcohol cues (Cohen's $d = 0.41$)
Pratt and Davidson (2009)	74 non-treatment seeking alcohol-dependent adults whose preferred beverage was beer	Stress was induced using the Paced Auditory Serial Addition Test (PASAT). Neutral condition was sitting quietly for the same length of time as the PASAT	Neutral cue was water. Alcohol cue was preferred beer brand in a glass behind a sliding door, when accessible, one could drink the beer	Within-subject design. CS measure was craving	There were no significant differences in alcohol craving between stress and neutral condition after cue exposure (Cohen's $d = 0.108$)
Ray (2011)	64 non-treatment seeking heavy drinkers	Stress imagery of stressful recent personal events; neutral imagery of recent neutral personal events	Exposure to water and alcohol beverages	Within-subject design. CS measure was craving	Presentation of alcohol cues increased alcohol craving and negative mood across both stress and neutral imagery. Alcohol cues produced greater increases in craving after neutral imagery when compared to stress imagery (Cohen's $d = 1.83$)

Note. AD = alcohol dependence, CM = coping motives, CS = cue sensitivity, PTSD = posttraumatic stress disorder.