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(Neuro)therapeutic Approaches in the Field of Alcohol Use Disorders

A Beck[1] · A Rosenthal[1] · M Auriacombe[2,3,4] · N Romanczuk-Seiferth[1]

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Abstract

Purpose of Review Alcohol use disorder (AUD) is a burdening chronic condition that is characterized by high relapse rates despite severe negative consequences. There has been a recent emergence of interest in (neuro)therapeutic intervention strategies that largely involve the detrimental change in mechanisms linked to addiction disorders. Most prominently, the latter include habitual decision-making, cue-induced behavioral tendencies, as well as the amplifying effects of stressful events on drinking behavior. This article discusses these learning mechanisms and modification thereof as possible targets of (neuro)therapeutic interventions for AUD.

Recent Findings Psychological therapies that target dysregulated neurocognitive processes underlying addictive behavior may hold promise as effective treatments for AUD.

Summary Despite the progression in psychological and neuroscience research in the field of AUD, many behavioral interventions fail to systematically integrate and apply such findings into treatment development. Future research should focus on the targeted modification of the aforementioned processes.

Keywords Alcohol use disorder · Treatment · Addiction · Habitual decision-making · Stress · Cue · EMA · Intervention

Introduction

Substance use disorders (SUD) are defined as problematic patterns of use associated with clinical impairment and persistent relapse overtime [1, 2]. Alcohol use disorder (AUD) is remarkable because it causes immense global health burden and financial costs and its treatment is problematic [1, 3]. Currently, the psychological treatment of post-acute AUD mainly comprises of motivational enhancement therapy, cognitive behavioral therapy, contingency management, as well as supervised patient group therapy [4].

However, effectiveness of current therapeutic approaches would benefit from better taking into account improved understanding of AUD underlying processes and their modification. Overall, addiction disorders in which substance intake is dysregulated [2] can be referred to as "pronounced preference disorders." Regardless of the addiction condition, substance intake is somewhat similar to other automatic actions based on preferences and reinforcing everyday experiences, but due to the pharmacological effect of the substance, the stimulus is particularly pronounced [5] and as such may contribute to the dysregulation of substance intake.

AUD and other addiction disorders are characterized by a gradual shift from initial goal-directed drug use mediated by the reinforcing and hedonic effects of the drug (regulated substance intake) to an increasing loss of control over drug intake (dysregulation), which thus becomes habitual, that is, automated and disconnected from its consequence, one behavioral outcome of which is compulsive use. One unique characteristic of addictive disorders is persistent relapse rates over time despite awareness of severe negative consequences [6]. Even

A Beck and A Rosenthal contributed equally to this work.

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✉ A Rosenthal
annika.rosenthal@charite.de

[1] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Charitéplatz 1, 10117, Berlin, Germany

[2] University of Bordeaux, Phenomenology and Determinants of Appetitive Behaviors (Addiction Team), Sleep, Addiction and Neuropsychiatry Laboratory (SANPSY), USR CNRS 3413, 146 Bis Rue Léo Saignat, 33076 Bordeaux, France

[3] Pôle Addictologie, CH Ch. Perrens and CHU de Bordeaux, 121 Rue De La Béchade, 33076 Bordeaux, France

[4] Center for Studies of Addiction, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, 3535 Market St, Suite 4000, Philadelphia, PA 19104, USA

in the face of severely aversive consequences, it can be nearly impossible to stop drug intake in spite of conscious decisions to reduce consumption or to remain abstinent [7, 8].

Despite that habitual and compulsive drug intake are to be differentiated, they can be triggered by drug-associated cues, acute stress events, or a priming dose of the drug [9]. In chronic problem drug users, conditioned drug cues gain incentive salience, whereas alternative reinforcers become less important [10–13]. Finally, drug addiction also involves negative reinforcement during withdrawal distress and early and long-term abstinence, which is defined as drug-taking that alleviates a distress-associated aversive emotional state [14], which may be a characteristic of craving as a diagnostic criterion [15].

However, some AUD patients are able to regain control over their alcohol intake, suggesting that the above-named mechanisms can be partly reversed or compensated [16••]. There has been a recent emergence of interest in (neuro)therapeutic intervention strategies that largely involve the detrimental change in learning mechanisms linked to addiction disorders [17]. This report aims at reviewing potential therapeutic targets that have been highlighted in recent AUD research. Most prominently, they include habitual decision-making, cue-induced behavioral tendencies, as well as the amplifying effects of stressful events on drinking behavior (see Fig. 1). We will also review intervention strategies that are designed to target the aforementioned processes.

Habitual Decision-Making

According to dual-process theories of addiction, alcohol consumption in addiction can be driven by an attentional bias as well as by a habitual approach toward drug cues in expense of initially goal-directed control [18]. Goal-directed action control supports flexible planning to promote desirable choices when facing potential actions and probabilistic consequences. On the other hand, habitual control encompasses the mere repetition of previously rewarded action without taking into account that the outcome value might have changed [19]. In context of this, preclinical research and human neuroimaging studies have related goal-directed and habitual action control to two separable neuronal systems [20, 21]. Habitual control mainly relies on the putamen, while the goal-directed system has been suggested to involve the ventromedial prefrontal cortex as well as the ventral striatum [22–24]; however, see Deserno and colleagues [25] for indication of ventral striatal activation in habitual control.

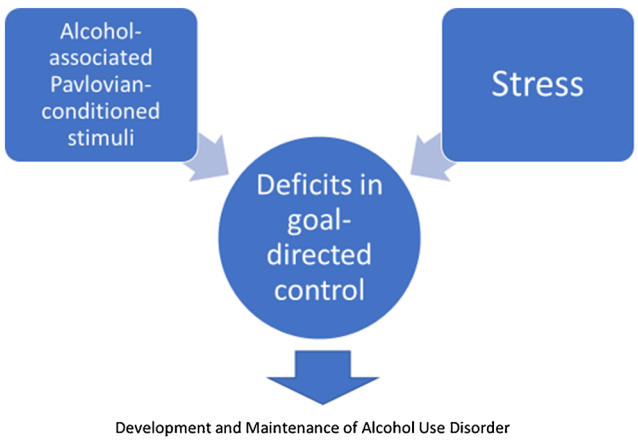

Fig. 1 Processes underlying the development and maintenance of alcohol use disorders

The shift from goal-directed to habitual behavior that is seen with disease progression might render individuals with AUD to be insensitive to aversive outcomes associated with alcohol use [26]. Furthermore, subjects with AUD might also be more insensitive to aversive events in general, as, e.g., could be shown in terms of a reduced loss aversion in comparison with healthy subjects [27]. In addition to this, craving and acquired (learned) habitual patterns of alcohol intake could aggravate the phases of early abstinence [28]. Regarding a controlled selection of goals in contrast to habitual drug intake, it was recently observed that an increased general tendency for habitual responding predicted poor treatment outcome only in the presence of high alcohol expectancies [24••]. Such biases can be modified by, e.g., systematically training habitual rejection of alcohol-related stimuli (e.g., pictures) [29]. Following training, a good treatment outcome was associated with reduced limbic activation elicited by alcohol-related pictures [30••].

In addition to lack of goal-directed reward choices, avoidance behavior is proposed to be impaired as well. Ersche and colleagues showed that patients with cocaine use disorder (CUD) show similarly increased habitual responding as AUD cohorts and furthermore failed to avoid aversive outcomes in a punitive learning task [26]. In terms of therapeutic implications, the authors state that impaired avoidance behavior, as well as habitual drug intake should be targeted and replaced by healthy habits. This approach is extended by Stock in a perspective article [31] arguing for the establishment of habit reversal therapy (HRT) in AUD. HRT embodies multiple components that aim at altering dysfunctional habits and has been proven to be efficacious in repetitive behavioral disorders [32]. Briefly, HRT encompasses an awareness training phase in which automatic behavioral tendencies are identified to then be replaced by competing (healthy) habits in the therapy phase. These factors are accompanied by generalization to relevant contexts and motivational techniques such as social support training or the review of inconvenience caused by the habit [33]. The establishment of adequate motivational support, as well as concrete long-term perspectives, has been shown to be essential in any treatment strategy that addresses automatisms in AUD [34].

In light of this, it was also observed that goal-directed decision-making is affected by increased life stressors [35],

underlining the strong potential of interventions aimed at altering stress-related effects on AUD. Overall, there is a prominent lack of therapeutic interventions that target the overreliance on habitual control in AUD directly. However, habitual alcohol use largely depends on instrumental conditioning with learned stimulus-response associations. This indicates that alcohol-associated environmental stimuli act as powerful motivators for recurrent alcohol intake [36].

Cue Reactivity

As an individual diagnostic criterion, craving is the most selective and specific across addictive disorders [15], but it is also an individual experience that varies over time and is elicited by exposure to different drug-related cues and autonomic responses, which can manifest as higher heart rate as well as higher skin conductance [37, 38] but predominantly trigger aversive responses such as tension, restlessness, and trembling [39]. In line with that, higher heart rate variability (HRV) during exposure to stress-primed alcohol cues was linked to relapse rates [40], while HRV might reflect increased active suppression of appetitive motivational responses in highly cue-reactive individuals [41, 42]. Others argue that physiological responses to alcohol cues are mainly unconsciously processed, as they were not correlated to self-ratings of arousal, valence, and craving [43]. The same study also linked shorter abstinence duration in AUD patients to an attenuated startle response toward alcohol cues [43]. Studies furthermore reported a positive link between display of alcohol cues and subsequent craving as well as alcohol consumption in heavy social drinkers [44, 45]. A promising approach to assess craving in a valid manner without biases associated with retrospective reporting is the so-called Ecological Momentary Assessment (EMA, e.g., see 46 for review). This method offers the opportunity to examine both craving and substance use with strong ecological validity by collecting real-time data in daily life and to identify relevant moderators of craving [47•].

On a neural level, relapse in AUD patients was also directly linked to cue-induced functional activation in the striatum, anterior cingulate cortex, as well as medial prefrontal cortex [48, 49]. Furthermore, examining functional correlation between brain regions active during a cue-reactivity task, Stroche and colleagues [50] found that prefrontal-striatal connectivity during cue reactivity was negatively related to craving and alcohol consumption, indicating a potential top-down control effect that limits craving.

It has been argued that alcohol cues affect subsequent drinking via a direct stimulus-response association [51–53]. In extension of this, neutral environmental stimuli can become associated with drinking and also reinforce alcohol intake [36].

One hypothesis is that such contextual stimuli directly stimulate the motivation to drink via Pavlovian-to-Instrumental Transfer (PIT): a behavioral phenomenon describing how Pavlovian-conditioned cues enhance instrumental behavior for rewarding outcomes (e.g., alcohol seeking and intake) [54, 55]. In a current study in alcohol-dependent patients, it was shown that there is an enhanced PIT effect on instrumental behavior using Pavlovian cues that have been passively associated with monetary reward and loss [56]. Furthermore, enhanced PIT was negatively related to goal-directed control, suggesting a strong common basis of Pavlovian inference and habitual control that might affect the course and maintenance of AUD [57].

Using alcohol-related stimuli in a PIT task, Schad and colleagues [58] showed that alcohol-related background stimuli inhibited the approach behavior in prospective abstinent alcohol-dependent patients, but not in healthy controls or prospective relapsing patients. This observation could indicate that subsequent abstainers acquired a successful way to deal with alcohol cues and that such behavior inhibition may be specifically trained in therapeutic interventions.

Despite these promising findings, the mechanism underlying approach avoidance behavior related to different Pavlovian stimuli is not known to date. However, it is known that in patients with AUD there is a bias toward action tendencies to approach alcohol and alcohol-related stimuli [59]. One method to assess such an approach bias, i.e., automated instrumental behavior in reaction to Pavlovian stimuli, is the so-called Approach-Avoidance Task (AAT, see 60). Here, patients are explicitly or implicitly asked to initiate approach or avoidance movements (pulling/pushing a joystick) in response to alcohol-related pictures. Wiers and colleagues [61] observed that heavy drinkers indeed showed strong automatic approach tendencies for alcohol (approach bias). Here, the so-called Approach Bias Modification (ABM), which uses a training version of the AAT, has been shown to be effective in the treatment of AUD: By using AAT training, patients' initial approach bias could be changed into an avoidance bias for alcohol-related stimuli [62]. This effect even generalized to untrained pictures, and patients showed better treatment outcomes in terms of reduced relapse rates 1 year later [60]. However, the underlying mechanisms of ABM are not fully understood (see 29).

Another psychological treatment approach that aims at diminishing the impact of cues (both contextual and specific) on drug intake and relapse is based on animal extinction research [17, 63]. The so-called cue exposure therapy (CET) operationalizes the prediction that conditioned responses to drug cues can be extinguished by prolonged non-reinforced drug cue exposure [64, 65]. One meta-analysis examined the effect of CET on abstinence or drug-use reduction across several studies and concluded the intervention to be ineffective for other substance use disorders [66], but significant effect

sizes indicated clinical efficacy in AUD [67–69]. In line with this, a more recent meta-analytic review indicated that AUD patients do benefit from CET, specifically on secondary outcomes such as drinking score, latency to relapse, and alcohol-induced cravings [70].

In neuroimaging studies, it was shown that CET reduced neural cue reactivity in the ventral and dorsal striatum [71, 72]. In extension to traditional CET, the so-called memory retrieval-extinction has been proposed as an augmentation. Based on fear extinction research in animals, it was shown that memories can be diminished if non-reinforced exposure takes place during memory consolidation [73, 74]. In a study combining human and rodent research, Xue and colleagues [75] showed that retrieval of drug-associated memories before the extinction phase led to decreased cue-induced craving as well as increased abstinence rates. Recently, research into CET has been extended by technological advances to improve the effects and accessibility of CET for AUD [76]. A gamified version of CET in combination with virtual reality (VR) was well received in a cohort of AUD patients [77], and another study could show that VR CET reduced craving [78]. A video-enabled live action CET showed a promising treatment outcome as well [79]. One study assessed if cognitive behavioral therapy was more effective when combined with CET and training of urge-specific coping skills or with aftercare as usual [80]. In addition, the deliverance of CET between group sessions and via a smartphone app was tested, and no difference in efficacy was found; however, also no additional benefit to cognitive behavioral therapy was indicated [80].

An additional line of research aims to enhance the efficacy of CET using pharmacological adjuncts like D-cycloserine, a partial N-methyl-D-aspartate (NMDA) receptor agonist shown to facilitate extinction learning in animal models of drug addiction [81]. While translating these findings to cue exposure in addiction revealed very heterogeneous results [82], at least some preliminary evidence indicate that DCS-augmented cue exposure reduced cue-induced BOLD activation in the ventral striatum [71] and subjective craving [83] in subjects with AUD.

Overall, there is ample information on the effects of drug-related cues on various addiction-related processes, and different interventional approaches such as ABM and cue exposure therapy have been developed based on this evidence. However, to date it remains unclear whether these approaches enhance treatment effects beyond standard interventions such as CBT.

Stress

Besides contextual (Pavlovian drug-associated) cues, stress has also been shown to induce drug-seeking behavior [84, 85]. Moreover, in a study by Seo et al. [86], stressful life events were associated with heavy drinking in early adolescence. Thus, the experience of stress may act as an internal cue for drug-seeking behavior in addictions, comparable with effects of drug-associated external cues. Further, stress exposure has a strong moderating influence on cognitive abilities, reward learning, risk-taking, reward responsivity, and decision-making [35, 87–90]. In particular, a recent study assessed the influence of stress exposure on behavior (i.e., button presses to earn junk food) induced by Pavlovian stimuli in a group of healthy controls [91]. Here, it was found that high levels of stress were associated with elevated responding in the presence of a cue associated with a non-rewarding outcome, whereas low levels of stress were associated with appropriate suppression of responding (inhibition) during presentation of this cue. Noteworthy, gender and age effects were not found so far in previous studies [56, 58, 92].

Moreover, stress has a high propensity to shift goal-directed behavior to more habitual behavior (e.g., 93). This phenomenon plays a key role in addictive behaviors: Although initially drugs are consumed to, for example, avoid discomfort or to relax (i.e., to achieve a certain goal), drug-taking behavior can become habitual without considering the outcome when intake is regularly repeated. Habitual behavior is then performed automated and largely independent of its consequences by simply repeating actions associated with past reward, while goal-directed actions are performed because they are expected to produce a certain (desirable) outcome [19]. Regarding the impact of stress, Schwabe and Wolf [93] observed that stress modulates the control of instrumental action in a manner that favors habitual over goal-directed action. In line with this finding, Friedel and colleagues [90•] observed that high chronic life stress reduced goal-directed and increased habitual decision-making in healthy subjects moderated by low cognitive capacity.

Although generally adaptive, these changes in the control of instrumental action under stress may promote dysfunctional behaviors and the development of mental disorders such as addiction.

Although there is evidence on the prominent role of stress in the course of addiction, surprisingly, only a few studies are focusing on stress reduction in this field of research. Based on mindfulness-based stress reduction, mindfulness-based interventions (MBIs) such as mindfulness-based relapse prevention (MBRP) [94, 95] or mindfulness-oriented recovery enhancement (MORE) [96], among others, target several pathological mechanisms in SUDs. Notably, there is support for the effectiveness of MBIs in reducing stress in the context of addiction: Measures of heart rate variability (HRV) are often used as an index of stress regulatory ability [97], while higher HRV in response to drug cues might indicate the need for higher regulatory effort [40]. In samples with SUDs, MBRP was associated with increased HRV in response to stress [98–100]. In AUD patients, participation in MORE compared

with a control intervention led to increased HRV recovery from stress-primed alcohol cues in AUD patients [101]. Other studies observed that 2 weeks of meditation training (integrative body-mind training) produced a significant reduction in smoking among a group of smokers while progressive muscle relaxation as an active control condition did not [102, 103].

Furthermore, in smokers, decreased hair cortisol was associated with mindfulness training, indicating a decrease in chronic stress [104]. Brewer and colleagues [105] assessed mindfulness training (MT) compared with cognitive behavioral therapy (CBT) in individuals with alcohol and or cocaine use disorder showing reduced psychological and physiological indices of stress during stress provocation in MT compared with CBT.

Likewise, Back and colleagues [106] observed significantly less stress-induced craving and stress-related responses (during stress provocation) and greater ability to resist urges to consume in subjects with SUD receiving a cognitive-behavioral stress management intervention in contrast to the comparison group. In pathological gamblers, a stress management program including relaxation breathing revealed a significant reduction of stress, depression, and anxiety symptoms as well as an increase of life satisfaction and a better daily routine compared with a waiting list control group [107]. A neuroimaging study associated mindfulness training in smokers with decreased neural activity within insula and amygdala during exposure to stress, which was in turn associated with the amount of cigarettes smoked at follow-up [108].

Another interesting instrumental learning approach for patients with AUD—which might also be used in stress regulation—is real-time fMRI neurofeedback (rtfMRI NF). By feeding back the neural activity in circumscribed brain regions to the patient while presenting alcohol cues, its goal is to enhance control over brain activation and related cognitive processes [109]. First study results indeed indicate a reduction of neuronal activity and craving in patients with AUD [109] and of striatal cue-reactivity in heavy drinkers by rtfMRI NF [110].

Conclusion

Several key mechanisms that control the course of AUD have been identified by a large body of research that has been continuously expanded over the last decade. Integration of this literature on habitual decision-making [20, 57], cue-induced behavioral tendencies [56, 92], as well as the amplifying effects of stressful events [86, 90] can provide a framework to identify and disentangle the relative contributions of these mechanisms to AUD. However, while there have been attempts to target these mechanisms to treat AUD, studies indicated mixed results. These discrepant results may be due to unidentified modifying variables, which may well be targeted using ambulatory assessment with EMA [16, 46, 47]. In light of these digital technologies and opportunities, mechanism-based interventions with the aim of (1) the promotion of goal-directed control, (2) modification of Pavlovian effects on instrumental behavior, and (3) reduction of stress to enhance cognitive control over drug urges can be tested within intense longitudinal datasets that also reflect differences in gender, age, social status, and cultural diversity within an essential future field of research [16••].

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Compliance with Ethics Guidelines

Conflict of Interest The authors declare no conflicts of interest in the production of this work.

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