Effects of Cue-Exposure Treatment on Neural Cue Reactivity in Alcohol Dependence: A Randomized Trial

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Background: In alcohol-dependent patients, alcohol-associated cues elicit brain activation in mesocorticolimbic networks involved in relapse mechanisms. Cue-exposure based extinction training (CET) has been shown to be efficacious in the treatment of alcoholism; however, it has remained unexplored whether CET mediates its therapeutic effects via changes of activity in mesolimbic networks in response to alcohol cues. In this study, we assessed CET treatment effects on cue-induced responses using functional magnetic resonance imaging (fMRI).

Methods: In a randomized controlled trial, abstinent alcohol-dependent patients were randomly assigned to a CET group ($n = 15$) or a control group ($n = 15$). All patients underwent an extended detoxification treatment comprising medically supervised detoxification, health education, and supportive therapy. The CET patients additionally received nine CET sessions over 3 weeks, exposing the patient to his/her preferred alcoholic beverage. Cue-induced fMRI activation to alcohol cues was measured at pretreatment and posttreatment.

Results: Compared with pretreatment, fMRI cue-reactivity reduction was greater in the CET relative to the control group, especially in the anterior cingulate gyrus and the insula, as well as limbic and frontal regions. Before treatment, increased cue-induced fMRI activation was found in limbic and reward-related brain regions and in visual areas. After treatment, the CET group showed less activation than the control group in the left ventral striatum.

Conclusions: The study provides first evidence that an exposure-based psychotherapeutic intervention in the treatment of alcoholism impacts on brain areas relevant for addiction memory and attentional focus to alcohol-associated cues and affects mesocorticolimbic reward pathways suggested to be pathophysiologically involved in addiction.

Key Words: Addiction, alcoholism, brain imaging, cue-exposure based extinction, cue-reactivity, fMRI

Alcohol dependence is associated with a high risk of relapse, often precipitated by exposure to alcohol-associated cues (1). Incentive-sensitization models of addiction (2) propose that during the development of substance dependence previously neutral stimuli like the sight and smell of alcohol become tightly associated with reinforcing drug properties. Thus, these stimuli become especially salient and, through associative learning processes, acquire the potential to evoke drug-like or drug-opposite responses. Such drug-associated responses, a phenomenon known as cue reactivity, have been observed in several studies concentrating on subjective, behavioral, and physiological levels (3,4). In support of the clinical significance of cue reactivity as a major trigger for relapse, recent findings suggest a strong association between this construct and compulsive drug taking (5,6).

Models of incentive-sensitization propose that the mesolimbic dopaminergic system represents the neural network mediating the increased incentive salience attributed to drug-related stimuli (2). During the last decade, great progress has been made in identifying these affected neural networks (7–11). Among the brain regions most commonly implicated in cue reactivity are the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the orbitofrontal cortex, as well as the insula, nucleus accumbens, amygdala, thalamus, and hippocampus. The magnitude of functional magnetic resonance imaging (fMRI) cue reactivity in reward-related areas has been found to be positively related to the intensity of self-reported drug cravings (8,12,13) and the amount of postrelapse alcohol consumption (5). Focusing on the mesolimbic system as the neurobiological cue-reactivity substrate, the present study examined whether a treatment intervention aiming to reduce cue reactivity has any objectively observable effects on neural mesolimbic activations in response to alcohol-related stimuli.

Based on the importance of conditioned drug-associated responses for the resumption of drinking, cue-exposure based extinction training (CET) was designed as a treatment approach to prevent relapse by attenuating conditioned responses through repeated exposure to alcohol without drinking (e.g., [14]). Although CET seems to be ineffective for other addictive disorders (see the review by Conklin and Tiffany [15]), several studies demonstrated that CET for alcohol-dependent patients reduced alcohol consumption and prolonged abstinence (14,15). For example, Monti *et al.* (16), Rohsenow *et al.* (17), and Sirtharthan *et al.* (18) report effect sizes in favor of CET ranging from .54 to .74. Consequently, the Task Force on Promotion and Dissemination of Psychological Procedures set up by the American Psychological Association concluded that CET is among the most effective treatment approaches for alcohol abuse and dependence (19). In addition, several, but not all, studies have also demonstrated a reduction of conditioned responses after CET (14,20) on subjective and physiological levels. While for tobacco dependence a reduction of cue-induced amygdala activation after CET was shown (21), to date no studies, to the best of our knowledge, have directly investigated the effects that CET might have on the functioning of the mesolimbic dopaminergic system in alcohol-dependent patients instead of assessing

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indirect measures of incentive salience. Thus, examining the mesolimbic dopaminergic system as a target region allows testing the hypothesis that CET impacts on mesolimbic pathways reducing conditioned drug-associated responses relevant for treatment outcome.

In this study, we used fMRI to study the effects of a 3-week CET program on cue reactivity elicited by alcohol-related visual stimuli. As CET is thought to attenuate conditioned drug-associated responses, it was hypothesized that larger reductions in fMRI cue reactivity, especially in reward-related areas such as the ventral and dorsal striatum, would be observed in CET patients relative to patients who underwent standard clinical treatment. As a second outcome measure, we used subjective craving, which was assessed during the scanning session. We hypothesized a larger decrease in subjective craving for alcohol in the CET group.

Methods and Materials

Participants

Between March 2008 and March 2009, 43 abstinent alcohol-dependent patients were recruited from the day clinic of the Department of Addictive Behavior and Addiction Medicine at the Central Institute of Mental Health in Mannheim, Germany. To be eligible for study participation, patients had to fulfill the following inclusion criteria: aged between 18 and 65 years, alcohol dependence according to DSM-IV, controlled abstinence for at least 3 days, and completion of medically supervised detoxification. Only right-handed subjects (handedness laterality quotient according to the Edinburgh Handedness Inventory [22] greater than 50) with a normal or corrected-to-normal vision (binocular visual acuity $\geq$ .8) were included. Exclusion criteria were Axis I or II psychiatric disorder according to DSM-IV (within the past 12 months, except alcohol or nicotine abuse or dependence), positive urine drug screening (opiates, cannabinoids, benzodiazepines, barbiturates, cocaine, amphetamines), current use of psychotropic or anticonvulsive medication (treatment of withdrawal symptoms with short-acting benzodiazepines or chlormethiazole had to be completed for at least 3 days, i.e., $> 5\times$ elimination half-life [t½]), renal insufficiency, epilepsy, suicidal tendency, pregnancy, and neurological or severe medical illness.

Each patient was randomly assigned to either the CET or control group. Patient allocation to treatment arms was based on a randomization code (blocked randomization, block size: 10, allocation ratio: 1/1) generated by a SAS (SAS Institute, Inc., Cary, North Carolina) procedure provided by the biometrician in charge of the project. After enrollment (M.K., A.R.) participants were assigned to their groups according to the randomization code stored in a sealed envelope (C.G., F.K.). Data from five participants were excluded from analysis because of heavy movement in the scanner ($>$ 3 mm in x, y, or z direction or $>$ 3° rotation in any direction). Eight patients dropped out because of relapse during treatment (three CET group, five control group). The final sample consisted of 15 patients in the CET group (9 male patients; age 50 $\pm$ 8 years, range 37–65 years) and 15 control patients (10 male patients; age 43 $\pm$ 9 years, range 27–57 years). Previous fMRI studies have shown that a sample size of about 12 to 14 subjects per group has sufficient power to obtain significant group activations as well as group differences in studies on cue reactivity (5,23). On average, patients in the CET group had consumed 131 $\pm$ 149 g of alcohol per day before admission (range 14–560 g/day), had been abstinent from alcohol for 10 $\pm$ 6 days (range 3–28 days), had been suffering from alcohol dependence for 16 $\pm$ 12 years (range 1–39 years), and had undergone 2 $\pm$ 4 previous detoxifications (range 0–13). In the control group, patients had had a mean daily alcohol intake before admission of 100 $\pm$ 91 g (range 10–287 g/day), had been abstinent from alcohol for 8 $\pm$ 4 days (range 3–16 days), had been alcohol-dependent for 13 $\pm$ 7 years (range 1–31 years), and had undergone 2 $\pm$ 5 previous detoxifications (range 0–16). The two treatment groups did not differ in pretreatment alcohol intake (p = .446), duration of abstinence (p = .337), duration of dependence (p = .505), or number of previous inpatient detoxifications (p = .318). The study was approved by the Ethics Committee of the University of Heidelberg. All participants provided written informed consent according to the Declaration of Helsinki.

Procedure and Cue-Exposure Based Extinction Training

Cue reactivity was assessed with fMRI before and 3 weeks after treatment onset. Before study inclusion, all patients completed medically supervised detoxification. During the following 3 weeks, they underwent clinical day-care treatment comprising health education and supportive therapy. Patients in the CET group additionally received nine standardized CET sessions over 3 weeks. To ensure standardization, CET was delivered according to a previously validated (20) treatment manual (24). The CET sessions were conducted by a clinically trained psychologist and supervised regularly to ensure that CET was provided according to the manual. Patients were exposed to their favorite alcoholic drink by handling the alcohol bottle, pouring a drink, and smelling the drink without consuming it. In the first CET session, patients developed a hierarchy of personally relevant situations that might trigger a relapse. To evoke conditioned drug-associated reactions (e.g., increased craving and physiological arousal) and to enable the patient to experience changes in these reactions over time during each session and over repeated sessions, patients imagined situations with increasing risk for relapse, while exposed to their preferred alcoholic beverage, over the course of the 3-week treatment. Each session lasted about 60 to 90 minutes and was only terminated when the patient reported a craving reduction to zero, which was achieved by all patients. However, for safety reasons, all sessions were scheduled for the morning to assure that patients spent some time in the day clinic facility before leaving for home and could easily contact a therapist in case of any further craving experience. Thus, CET was standardized regarding the exposure procedure to the preferred alcoholic beverage and individualized regarding procedure duration and imagination of individual situations. The control group received standard clinical day-care treatment and did not undergo a control procedure like attention training or dummy exposure. However, as CET was provided during the normal daily routine comprising other therapeutic supportive contacts, the actual therapeutic treatment amount did not differ between groups.

Assessment of fMRI Cue Reactivity

Although the CET procedure focuses on individual cues, cue-reactivity reduction, in general, is desired for its clinical efficacy. Hence, we used the same picture set for all patients, which is the common procedure to avoid habituation and to ensure comparability between participants. Sixty alcohol-related and 45 neutral stimuli were presented using a blocked design. Each block consisted of five stimuli, each presented for 4 seconds. Alcohol-related pictures were taken from a validated picture series (25). Neutral control cues were taken from the International Affective Picture System (26). Following each block, the participants rated the intensity of their alcohol craving on a visual analogue scale ranging from 0 (no craving) to 100 (extremely extensive craving). Task duration amounted to 12 minutes. Examples of the visual stimuli are provided in Figure 1.