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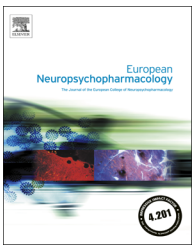

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Sustained incentive value of heroin-related cues in short- and long-term abstinent heroin users

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Abstract
Models of addiction and addiction memory propose that drug-associated cues elicit incentive effects in drug users, which play an important role in maintenance of drug use and relapse. Incentive effects have been demonstrated for smoking and alcohol-related cues but evidence for heroin-related cues has been inconclusive. Furthermore, it is unknown whether appetitive effects of heroin-related cues persist after prolonged abstinence, although heroin addiction is known to have high relapse rates. Therefore, we investigated implicit and explicit valence of heroin-related cues in dependent users at different stages of abstinence using affective startle modulation. In *Study I*, 15 current heroin users were measured before and after detoxification. Correspondingly, 15 healthy control participants were tested twice at an interval of 14 days. In *Study II*, 14 long-term abstinent heroin users were additionally measured in a single session. Implicit processing of drug-related stimuli was assessed using affective startle modulation by pictures of heroin and smoking scenes. Explicit reactions were measured using ratings of valence and craving. In contrast to controls, heroin-dependent participants showed a clear reduction of startle response during heroin-related pictures ($p<0.05$). Detoxification did not significantly change their startle responses to heroin-cues. No difference between non-detoxified current and long-term abstinent heroin users was found in implicit reactions to heroin-cues, whereas explicit measures differed between both groups (all $p<0.05$). After detoxification and even after prolonged abstinence, heroin cues still exert implicit appetitive effects in heroin users. This implies that drug-induced adaptations of reward circuits are long-lasting, resulting in a highly stable addiction memory.

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1. Introduction

Drug dependence, opiate dependence in particular, can be considered as a chronic relapsing disorder (Hser et al., 2001). Models of addiction propose that cue reactivity (i.e. elicitation of conditioned responses on psychological, physiological, and behavioral levels by drug-associated stimuli) is of particular importance in the maintenance of drug use and relapse (Carter and Tiffany, 1999; Fatseas et al., 2011). Traditional theories of drug cues hold that drug-associated stimuli evoke conditioned reactions that trigger withdrawal-like and aversive responses (Koob et al., 1997; Wikler, 1973). More recently, there is evidence that drug-associated cues may rather be processed as appetitive leading to the same behavioral and neurobiological responses like the drug itself (Dempsey et al., 2007; Geier et al., 2000; Mucha et al., 2000). Moreover, the incentive-sensitization theory proposes that drug consumption produces incremental neuroadaptations in the mesolimbic dopamine pathways, rendering them hypersensitive to drugs and drug-associated stimuli (Robinson and Berridge, 2000). This sensitization turns the act of drug taking and stimuli associated with it into powerful incentives that produce a strong feeling of ''craving'' for the preferred drug. Craving commonly refers to the subjective experience of wanting to use a drug (Tiffany and Wray, 2012) and the urge to re-experience the effect of a psychoactive substance (UNDCP/WHO, 1992).

This is in line with multiple theories of addiction memory, which propose shared mechanisms between memory, learning, and addiction (Berke and Hyman, 2000; Hyman and Malenka, 2001; Hyman et al., 2006; Kelley, 2004; Robbins and Everitt, 2002; White, 1996). Repeated pairings of drugs and environment are supposed to produce long-term, maybe permanent, neuroadaptive effects in motivational networks that lead to the establishment of compulsive drug-seeking habits (Kelley, 2004; Robbins and Everitt, 2002). These associations and the craving elicited by drug-related stimuli might be in part unconscious (Tiffany, 1990). Drug memories are therefore supposed to be long-lasting and implicit. This assumption is consistent with high relapse rates among heroin users following treatment (O'Brien, 1997).

A well-established non-subjective method to measure the implicit valence of drug-associated cues is the affective startle modulation (Geier et al., 2000; Rehme et al., 2009). The acoustic startle reflex (ASR) is a solid marker of emotional reactivity (Lang et al., 1990) and is elicited by unexpected, intense environmental stimuli such as a sudden, loud noise. The affect-modulated startle methodology has been repeatedly used in drug research by including photographs of drug paraphernalia or drug intake rituals and measuring the suppression of the startle response by drug-related scenes relative to neutral scenes (referred to as cue-related startle suppression, CSS). In general, these studies confirmed incentive theories because they consistently reported CSS in addicted users of alcohol or nicotine while viewing drug-related cues (Cinciripini et al., 2006; Dempsey et al., 2007; Geier et al., 2000; Mucha et al., 2000). Enhanced attentional processing of heroin cues and cue-induced reactivity have been demonstrated for heroin users with other methods, like Stroop tasks and electrodermal responses (Franken et al., 2000; Lubman et al., 2008), and some of these found that cue reactivity might be a predictor for future heroin use and relapse after treatment (Fatseas et al., 2011; Lubman et al., 2009; Marissen et al., 2006). However, the implicit valence of heroin cues before and after detoxification and withdrawal therapy was not investigated so far. Furthermore, it is unknown whether heroin cues elicit appetitive effects in long-term heroin-abstinent individuals. However, sustained appetitive value of drug-related cues might be a driving force underlying the high relapse rates in heroin addiction (Carter and Tiffany, 1999; Fatseas et al., 2011).

Hence, we conducted two studies investigating the implicit valence of drug-related stimuli in different states of abstinence. In Study I, we analyzed the response to heroin-related cues in current heroin-dependent participants before and after a two week detoxification program, as well as in control participants tested within the same time interval. Smoking cues were used because of the common co-use of nicotine in heroin-dependent patients. For the same reason, for the control group only smokers were recruited. ASR was evoked during the presentation of positive, negative, and neutral pictures from the *International Affective Picture System* (IAPS) (Lang et al., 1997) and drug-related cues in order to assess the implicit valence of stimuli. The subjective evaluation of the stimuli was measured by ratings of valence and craving. According to sensitization and addiction memory theories, we hypothesized that heroin cues have appetitive effects in heroin-dependent participants before and after detoxification.

The aim of Study II was to investigate the influence of successful long-term abstinence on affective processing of heroin-associated cues. Because of the significance of drug-related cues in relapse (Carter and Tiffany, 1999; Fatseas et al., 2011), it is important to investigate whether a history of opiate use is associated with persistent implicit memories and enhanced cue-reactivity or if processing changes after successful abstinence. Therefore, a group of long-term abstinent heroin users was compared with current heroin users before detoxification and controls. Here, we expected long-term abstinent heroin-dependent participants to be more similar to current opiate users than to controls in their implicit reactivity towards heroin cues, as the incentive sensitization theory and addiction memory models posit memory traces to be persistent.

2. Experimental procedures

2.1. Participants

Study I was carried out with two groups: 15 currently heroin-dependent participants and 15 healthy participants with no history of opiate use (Table 1). Heroin-dependent participants were enrolled in a residential detoxification program at the Department of Psychiatry of the University of Bonn, Germany. Intravenous heroin dependence was diagnosed following the Diagnostic and Statistical Manual-IV (DSM-IV) criteria (American Psychiatric Association, 1994). Detoxification therapy was standardized by treatment with methadone (up to 20 mg/day), which was decreased within 8–12 days of inpatient treatment. None of the patients in the detoxification program received methadone maintenance treatment prior to detoxification. The control group was recruited from the general population by advertisement.

Study II compared a non-overlapping sample of 14 long-term abstinent heroin users (assessed once) with the 15 heroin-dependent