

Human Laboratory Settings for Assessing Drug Craving; Implications for the Evaluation of Treatment Efficacy

Zahra Alam Mehrjerdi ¹, Hamed Ekhtiari ^{1,2*}, Azarakhsh Mokri ^{3,4}

1. Neurocognitive Laboratory, Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran.

2. Translational Neuroscience Program, Iranian Institute for Cognitive Sciences Studies (ICSS), Tehran, Iran.

3. Clinical Department, Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran.

4. Department of Psychiatry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Research on assessing craving in laboratory settings often involves inducing and then measuring craving in subjects. Cue-induced craving is studied in laboratory settings using the cue reactivity paradigm, in which drug-related photos, videos, evocative scripts, olfactory cues, and paraphernalia may induce craving. Cue-induced craving evoked by drug-related stimuli could be associated with relapse and recurrence of drug addiction. In this article, the authors review different methods of assessing craving in laboratory settings and explain how human laboratory settings can bridge the gap between randomized clinical trials (RCTs) and animal models on pharmacological treatments for drug dependence. The brief reviewed literature provides strong evidence that laboratory-based studies of craving may improve our understanding of how subjective reports of drug craving are related to objective measures of drug abuse and laboratory settings provide an opportunity to measure the degree to which they co-vary during pharmacological interventions. This issue has important implications in clinical studies.

Introduction

Studies show that there is a pivotal relationship between craving and addiction (World Health Organization, 1955). Although craving has a complexity in definition but craving for a drug may be defined as a strong desire to crave, acquire and use drug, and may be evoked even after periods of sustained abstinence by exposure to stressful situations, to drug, or to environmental cues previously associated with drug use (Mahoney et al., 2007; Sinha, 2001).

Research on craving in controlled laboratory conditions is an important concern for scientists because of

its relationship with relapse and recurrence of addiction. Studies show that reactivity to drug-related cues in laboratory settings (cue-induced craving) is obviously observed in drug addicts (Rohsenow et al., 1991). In learning and memory models, cue-induced craving is defined as a classical conditioning situation in which previously neutral cues obtain prominent salience as conditioned stimuli through repeated pairings with a drug (Robinson & Berridge, 1993). Once this association is formed, exposure to the conditioned stimulus can easily elicit a conditioned craving even when the desired drug is not available (O'Brien, 2005). In recent decades, scientists have studied cue-induced craving in different drug abusers using the cue reactivity paradigm and with different drugs including alcohol (Drummond et

* Corresponding Author:

Hamed Ekhtiari, MD.,

Neurocognitive laboratory of Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences. Address: No.669, South Karegar Ave, Tehran, 1336616357, Iran, Tel/Fax +982155421177.

Email: h.ekhtiari@razi.tums.ac.ir

al., 1990), nicotine (Tiffany & Drobles, 1990), cocaine (Ehrman et al., 1992), methamphetamine (Ekhtiari et al., 2010a; Toliver et al., 2010) and opiate (Childress et al., 1994).

Craving can be evoked with different cues in laboratory settings including verbal cues, videos (Ekhtiari et al., 2010b; Ren et al., 2009; Shi et al., 2008), imagery evoking scripts (Sinha et al., 2000), pictures (Ekhtiari et al., 2008; Mokri et al., 2008) and paraphernalia (Yu et al., 2007). Such cues have been shown to induce drug craving (Sinha et al., 2000), physiological changes such as changes in level of blood pressure, heart rate, withdrawal signs (Carter & Tiffany, 1999), and psychological changes such as changes in affect and mood (Fox et al., 2005) that may substantially contribute to relapse and impact treatment procedure negatively (Sinha et al., 1999).

Methods for Assessing Drug Craving

Craving can be assessed with different methods in laboratory settings. These methods are mainly divided in to two approaches including self-report measures and non-verbal measures respectively.

I. Self- Report Measures

Self-report measures such as questionnaires can obviously provide important information about an individual's craving, and play a major role in the measurement of craving (Tiffany et al., 2000). Questionnaires such as Desire for Drug Questionnaire (DDQ) and Obsessive Compulsive Drug Use Scale (OCDUS) are two examples of these questionnaires which can be used in assessing craving (Franken et al., 2002; Anton et al., 1995).

II. Non-verbal Measures

Non-verbal measures are other approaches that can be used to measure craving. Non-verbal measures of craving include drug reinforcement "proxies", drug self-administration, cognitive processing, neurobiological responding, psychophysiological responding, startle reflex, and expressive behavior respectively.

1. Drug Reinforcement Proxies

The degree to which a desired drug is reinforcing can be used as a measure of craving. The level of drug reinforcement has been assessed using several measures; often they involve assessment of choice behavior leading

to drug administration. In this approach, craving can be inferred by determining the amount of work or pain that an animal or a human subject will assume in order to obtain a desired drug (Gardner & Lowinson, 1993). Becker and Murphy, (1988) and Loewenstein (1999) have attempted to describe the perceived reinforcement value of drugs by asking subjects to choose between drug use and varying amounts of money (Griffiths et al., 1993). Presumably, the greater the value attributed to drug use, the greater the drug craving. This method can be considered in studies related to craving research.

2. Drug Self-Administration

Drug use can be also influenced by many stimulants other than drug craving. Several measures of drug use have been employed to elicit craving in laboratory settings. One approach is to measure the time that elapses from the moment that a subject is permitted to engage in drug use until initiation of drug use (latency). Other measures of drug use also have been used such as cigarette puff frequency, strength and volume, length of cigarette puff, and interpuff interval (Kashinsky et al., 1995). Latency to first cigarette puff may be an important component of drug use behavior that is related to drug craving.

3. Cognitive Processing

Long term drug use interferes with various brain functions and cognitive aspects of human. As a cognitive processing, attention can be automatically directed towards drug-related cues. Attentional bias in drug addicts is shown by the involuntary preoccupations that addicts tend to have for these cues. As an implicit cognitive processing, attentional bias is related to craving (Franken et al., 2003). Drug-related memories can also play an implicit role in evoking craving. Implicit drug memories are automatic effortless processes which take place without intention or control and can operate without awareness (Tiffany, 1990). Both implicit and explicit memories may lead to relapse in drug use.

Attention tasks can be used to assess craving by measuring reaction times (RTs). Studies using both smokers and alcoholic subjects have shown increases in secondary RTs during high craving periods, relative to non-craving baseline periods (Cepeda-Benito & Tiffany, 1996; Juliano & Brandon, 1998). Other tasks include Addiction Stroop (Cox et al., 2006), the visual probe task (Ehrman et al., 2002) and attentional cueing tasks (Franken et al., 2000). Another type of attention task measures the direct monitoring of participants'

eye movements while drug-related cues are presented (Rosse et al., 1993, 1997). Cognitive tasks have been proven useful in suggesting memory structures associated with craving as well as cognitive processes that may change during craving.

4. Neurobiological Responding

Functional imaging techniques like Single Photon Emission Computed Tomography (SPECT), functional Magnetic Resonance Imaging (fMRI), and Positron Emission Tomography (PET), have created opportunities to study the underlying neural mechanisms of drug addiction and addictive behaviors related to craving. Measures of glucose metabolism e.g. using PET scans with human subjects have revealed metabolic increases during craving manipulations in some brain structures associated with both emotional (e.g. amygdala) and cognitive (e.g. hippocampus) aspects of memory (Everitt, 1997). Exposure to drug cues increases activity in the amygdala and regions of the frontal cortex (Kilts et al., 2001; Grant et al., 1996). Nevertheless, it is important to recognize that imaging studies can only show that a specific craving manipulation produces increases in brain activation. Positron emission tomography (PET) studies have also shown strong correlations between the dorsal striatum region and drug cue-induced cocaine craving (Volkow et al., 2006). Increased stress, cue-induced craving and compulsive drug-seeking states in addicted individuals are associated with increased activity in the striatum region, but decreased activity in specific regions of the cingulate and prefrontal cortex, and related regions involved in controlling impulses and emotions (Li & Sinha, 2008).

Neurobiological changes may be correlated with craving, but like other psychophysiological measures, these changes do not necessarily result in craving (Van Orden & Paap, 1997). It should be noted that research using neuroimaging methodology to study craving is in earlier stages of development and more research should be conducted on the neural circuitry of craving.

5. Psychophysiological Responding

Changes in blood pressure, heart rate, skin conductance, skin temperature, and salivation have been included in craving studies, although the pattern of physiological responding has differed (Glautier et al., 1992). These measures have less vulnerability to conscious control and thus may be more sensitive than self-report measures to detecting craving (Baker & Brandon, 1990) but psychophysiological measures have been criticized

for a number of reasons. Psychophysiological systems serve functions that are independent of a motivation for drug use. In addition, certain physiological responses to drug use, or even to situations associated with craving, can be unrelated to a motivation to use the drug. Further, it is not manifest what patterns of psychophysiological responses ought to be related to drug craving (Niaura et al., 1988; Tiffany, 1990).

6. Startle Reflex

Startle reflex is also used in laboratory investigations to assess craving. Positive aspects of measuring startle response in studies of craving include its relative ease of measurement, noninvasiveness, and reflexivity which reduce the likelihood of response biases and good temporal stability. A negative aspect of this method is a lack of specificity. It should be noted that as more data are collected, the role of startle reflex in craving assessment will be better understood.

7. Expressive Behavior

Facial expressive behavior is an important measure of emotional responses (Barlow, 1988) which may be useful for measuring craving. Facial signals may reflect craving-related affect or a measure of craving. The Facial Action Coding System (Ekman & Friesen, 1978) can be used to code participants' responses to smoking cues under controlled conditions. An alternative measure of facial muscle activity is facial electromyography (EMG), which has been also used in studies of craving (Elash et al., 1995; Drobles & Tiffany, 1997) but using any of these measures of expressive behavior must be conducted in laboratory settings in which craving is induced and controlled laboratory conditions are employed.

Limitations in Animal Model Studies

An animal model refers to an experimental preparation developed for the purpose of studying a condition found in human subjects. The main assumption is that there is homology, or at least analogy, among the physiology and behavior of different species and hence extrapolations can be made from animal cases to human subjects (Russell, 1964). Descriptions of situations in which human individuals use drugs or relapse to drug use support the argument that the relationship between drug craving and drug use is not the same. Animal model studies of craving cannot completely explain craving and drug use in humans because drug users consume drugs even in the absence of drug craving and often drug craving does not result in using drug despite drug

availability (Childress et al., 1988). It should be noted that drug craving is a multidimensional issue which has subjective, behavioral, physiological and neurochemical aspects in humans but animal models and measures cannot assess the different aspects of craving. As a result, the uses of converging measures are essential for elucidating the environmental and biological determinants and correlates of drug craving.

Laboratory Settings for Assessing Craving

One of the main methods to study craving in drug abusers is controlled laboratory conditions. Laboratory settings create controlled conditions for scientists to conduct extensive research into craving. Improved instruments have been developed for assessing the severity of craving and these new rating scales have appropriate reliability in measuring and assessing craving (Bohn et al. 1995; Singleton et al. 1995) especially in laboratory settings. In a laboratory setting, different techniques for inducing and assessing craving can be used including exposing subjects to a drug, exposing subjects to visual representations of a drug, manipulating the subjects' mood states, and controlling environmental settings respectively. In these settings, the intensity of craving can be rated by the subjects themselves or can be measured through behavioral observations or the measurement of some physiological responses. Moreover, some studies related to drug craving can be conducted only in laboratory settings and these settings provide specific conditions for measuring craving which are similar to real environmental settings. For example, brain-imaging studies can only be performed in a laboratory setting because it is not possible to obtain images of individuals' brain activities while they are following their daily works or laboratory-based techniques that induce stress have been shown to elicit increased self-reported craving in some of drug abusers (Sinha et al., 1999). Such analyses require reliable methods for inducing and assessing craving which can be controlled in laboratory settings.

Discussion

Drug craving plays an important role in addiction. The research reviewed above points to the fundamental problem of craving evoked by drug-related cues which could play an active role in relapse and interrupting abstinence and treatment procedure of addiction. It should be noted that deficit in craving prevention may contribute to a number of related psychological and behavioral problems that are associated with drug abuse and could prolong for months and may need extensive therapy

for years which is still subject to further studies for researchers in Iran. Research on cue-induced craving in laboratory is essential in addiction studies because it may contribute to the continuation of drug use in active drug abusers and the occurrence of relapse in detoxified abusers (Everitt, 1997). Study on drug craving in laboratory is an important concern for researchers because human laboratory settings provide controlled experimental conditions and well-equipped environments for studying craving.

Further, it is important to develop improved methods and tools for reliably measuring craving as well as new and valid approaches for inducing craving in controlled human laboratory settings to assess craving. Only when such tools are available, researchers can address studying craving. Human laboratory studies document that exposure to drug-related stimuli which may include places and people associated with drug use or drug paraphernalia such as pipes, and in vivo exposure to drug itself can result in increased drug craving and physiological reactivity (Carter & Tiffany, 1999). Exposure to negative affect, stress or withdrawal-related distress has also been associated with increases in drug craving and cue reactivity (Sinha, Catapano & O'Malley, 1999; Sinha, Fuse & Aubin 2000). Human laboratory models provide an appropriate opportunity to test these hypotheses in humans and translate the understanding of the association between craving and relapse susceptibility from basic science models of relapse to the clinical context.

Craving assessment is crucially important, because craving is a useful concept that may help clinicians and researchers evaluate treatment success and predict relapse. Improved measurement of craving therefore may lead to more accurate relapse predictions and, subsequently, to more effective treatment and clinical care.

Developing human laboratory studies can model drug effects, drug self-administration and desire, craving and urges for drugs. Valid and reliable laboratory models that would allow understanding drug seeking and relapse susceptibility can provide translation of identified pre-clinical mechanisms of drug craving to the development and testing of novel treatment interventions in humans. Achieving these objectives in laboratory studies would contribute to identifying clinical markers of drug craving that could then be targeted for treatment development. This approach is a cost-effective and efficient way to facilitate both understanding the mechanisms underlying craving and relapse and to identify promising treatment targets.

A better understanding of those mechanisms in human laboratory settings can bridge the gap between randomized clinical trials (RCTs) and animal models of craving, in turn, which could lead to improved behavioral and pharmacological approaches for the treatment of drug dependence. Having validated a human laboratory model with effective provocation methods and reliable measures of drug craving, is necessary to test novel pharmacological agents that may decrease cue-induced drug craving. One of the key advantages of using human laboratory models for this purpose is that they provide a cost-effective and efficient way to assess new approaches prior to undertaking large-scale clinical trials. In laboratory settings, we can examine craving by provoking it through a variety of means, such as presentation of drug-related cues, and actual drug use that would be effective in eliciting craving like cue-exposure techniques. However, individual differences in who responds to cue, drug use and under what circumstances should be studied (Sinha and O'Malley, 1999). Advances in the assessments of craving through instruments development provide important tools with sensitivity in detecting changes in substance use behaviors for future research. Laboratory paradigms also provide important and potentially potent methods for studying craving.

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