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# Role of Environmental Factors in Cocaine Addiction

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**Abstract:** Decades of experimentation with a variety of pharmacological treatments have identified some effective therapies for heroin addiction but not for cocaine addiction. This may be due, at least in part, to our incomplete understanding of the factors involved in the differential vulnerability to these addictions, which are often considered mere variations of the same disorder. Indeed, the preference for one drug or another has been variously attributed to factors such as drug availability or price, to the addict's lifestyle, or even to chance. Yet, there is evidence of substance-specific influences on drug taking. Data from twin registries, for example, suggest that a sizeable portion of the variability in the susceptibility to drug abuse is due to environmental factors that are unique to opiates or to psychostimulants. Very little is known about the nature of these environmental influences. We report here original data, based on retrospective reports in human addicts, indicating that the setting of drug taking exerts a differential influence on heroin versus cocaine use. We also review additional clinical and pre-clinical data pointing to fundamental differences in the way in which the environment interacts with cocaine relative to heroin and other addictive drugs. These findings - as well as other evidence, including the lack of pharmacological treatments effective for both cocaine and heroin addiction - support the notion that much is to be gained by taking into account the substance-specific aspects of drug addiction. At a therapeutic level, for example, it appears reasonable to propose that cognitive-behavioral approaches should be tailored in a substance-specific manner in order to allow the addict to anticipate, and cope with, the risks associated to the various environmental settings of drug use.

**Keywords:** Drug Addiction, Drug Abuse, Heroin, Cocaine, Setting, Environment, Context, Stress.

## INTRODUCTION

The statistics concerning the prevalence of drug abuse and drug addiction are notoriously slippery because of the difficulties in collecting reliable information on the use of illicit substances (the definition of "illicit", furthermore, depending on local legislation). Nevertheless, according to the 2012 World Drug Report by the United Nations Office on Drugs and Crime [1], it appears that, at a global level, cocaine ranks fourth among all classes of illicit drugs, with an annual prevalence in the population aged 15-64 estimated at 0.3-0.5% in 2010. Users of cannabis are estimated at 2.6-5.0% of the world population, users of opiates/opioids at 0.6-0.8%, and users of amphetamine-like drugs at 0.3-1.2%. The major markets for cocaine continue to be North America (1.6% in 2010), Europe (1.3%), and Oceania (1.5-1.9%). The countries with the highest prevalence are Spain, 2.7%, the United Kingdom, 2.5%, the United States, 2.2%, and Italy, 2.1% [2]. The figures for the lifetime prevalence of cocaine use are more than three times higher. For example, about 4.3% of the European population aged 15-64 used cocaine at least once in the lifetime (versus an annual prevalence of 1.2%), with national figures varying from 0.1% to 10.2% [2]. The European countries with highest lifetime prevalence were Spain (10.2%), United Kingdom (8.8%), Italy (7.0%), and Ireland (5.3%). At the other end of the spectrum there were Greece (0.7%), Lithuania (0.5%), Malta (0.4%), and Romania (0.1%).

Thus, the overall proportion of the world population who ever used cocaine appears to be relatively small and that of regular cocaine users even smaller. Furthermore, it is well known that only a minority of cocaine users develops a substance use disorder, as defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) of the American Psychiatric Association [3]. Little more than 15% of cocaine users, for example, progress from controlled to compulsive use [4, 5]. When expressed in absolute terms, however, these apparently modest percentages translate into staggering figures: about 30 millions of cocaine users and several millions of cocaine addicts worldwide, the great majority of which live in the United States and Europe.

At a global level, the prevalence of cocaine use has changed relatively little in the past decades but with important geographical differences. In the United States, the annual prevalence of cocaine use in the population aged 12 and above reached an all-time high of about 6% in the late 1970s and early 1980s, declined to 2-3% in the mid-1990s, and remained around these levels, with shorter-term fluctuations, in the following years [1]. In contrast, over the same period, cocaine use has increased several folds in Europe (from about 0.3% in 1990 to about 1.2% in 2006-2011) and Oceania. Thus, it is reasonable to assume that cocaine will continue to represent a significant health and social problem in the near future [1, 2]. The enormous size of the total retail market for cocaine, which was estimated at US$85 billions in 2009 [1], is sufficient per se to convey the implications of cocaine abuse in terms of organized crime and law enforcement challenges.

Unfortunately, despite the progresses made in the last decades, effective treatments for cocaine abuse are still not available, as discussed in the following section. This lack of success might have been, at least in part, the consequence of having paid little attention to the substance-specific aspects of drug addiction [6]. We report here new data indicating fundamental differences between cocaine and heroin use in human addicts. We also review additional preclinical and clinical findings pointing in the same direction. This evidence may help researchers in their efforts at identifying new and more effective treatments for cocaine addiction.

## THERAPEUTIC APPROACHES TO THE TREATMENT OF COCAINE USE DISORDERS

To understand the possible reasons for the current dearth of therapeutic options for the treatment of cocaine abuse and cocaine

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addiction, it should be taken into consideration the conceptual framework surrounding the search for therapies. Substance use disorders include a variety of clinical conditions whose common denominator is the loss of control over the intake of psychoactive substances (DSM-IV-R) [3]. The neurobiological bases of these disorders are still poorly understood, although we know a great deal about the mechanisms of action of addictive drugs. In the late 1980s, it was shown that virtually all abused substances increase dopamine levels in the terminal regions of the meso-telencephalic dopaminergic system [7], a circuitry thought to play a pivotal role in drug reward [8, 9]. Different drug classes facilitate dopamine transmission through distinct mechanisms of action. Psychostimulant drugs, such as cocaine and amphetamine, increase dopamine overflow by binding the dopamine-reuptake transporter [10-12] whereas heroin and morphine and other opiate agonists facilitate dopaminergic transmission by binding mu-opioid receptors in the ventral tegmental area and the substantia nigra of the midbrain, hence disinhibiting the dopamine-releasing neurons originating in these regions [13, 14]. Later research has focused on the neurobiological consequences of chronic exposure to addictive drugs. It has been shown, for example, that repeated exposure to psychostimulants or opiates in rodents induce: 1) increased expression of tyrosine-hydroxylase, the rate-limiting enzyme of dopamine synthesis in the ventral tegmental area, 2) increased expression the transcription factor cAMP response element binding (CREB) protein and Δ-FosB in the ventral tegmental area and nucleus accumbens, 3) sensitization of drug-induced dopamine and glutamate overflow in the nucleus accumbens), and 4) long-term potentiation (LTP) of glutamatergic transmission in the ventral tegmental area [15-22].

The major drive behind the research summarized above was represented by a substantially "unitary" notion of drug addiction. This approach has been dominant since 1950, when a report by an Expert Committee ("on drugs liable to produce addiction") of the World Health Organization [23] defined drug addiction as "a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include: (1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) a tendency to increase drug intake; (3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug." It is not difficult to see, how the emphasis on phenomena such as tolerance (and the consequent need to increase the dose) and physical dependence (and the relief of withdrawal syndrome) was due to the almost exclusive focus on opiate addiction.

In turn, the identification of shared substrates for the acute and long-term effects of addictive drugs has led to ever more refined unitary models of drug addiction, starting with the influential psychomotor stimulant theory of addiction proposed by Wise and Bozarth in 1989 [24]. This approach has remained substantially unchallenged until today. The four main neurobiological theories of drug addiction, albeit focusing on different core processes - incentive sensitization [16], hedonic allostasis [25], aberrant learning [26], and fronto-striatal dysfunction [27, 28] - all argue for a unitary account of opiate and psychostimulant addiction. Also the therapeutic approaches to drug addiction have not changed substantially in the past decades, representing the translation of unitary models into therapeutic strategies: treatment of overdosing, replacement treatments (to achieve "detoxification" or "harm reduction"), blockade of drug rewarding effects, and relapse prevention. These aims were obviously identified on the basis of the characteristics of heroin addiction. The implicit assumption was that the same strategy would equally work for all classes of addictive drugs, and in particular for cocaine. Yet, the therapeutic overlap between heroin and cocaine addiction is negligible, as briefly discussed in the following.

**Treatment of Overdosing**

While heroin overdosing results in respiratory depression and coma, easily treated with mu-opioid receptor antagonists (i.e., naloxone or naltrexone), there is no equivalent treatment for cocaine overdosing, despite attempts at developing therapeutically viable anti-cocaine catalytic antibodies and cocaine esterases [29-33].

**Replacement Treatments**

Replacement therapy is used to achieve either "harm reduction" (in maintenance treatment) or "detoxification" (with progressive reduction in the dosage of the replacement drug). Detoxification is often a precondition for admission in a variety of pharmacological and non-pharmacological treatment programs for opiate addiction. As pointedly noted by Collins and Kleber [34], "current approaches to detoxification continue to be plagued by patient discomfort, high dropout rates, and high relapse rates."

Street heroin can be substituted for by long-acting full or partial agonists to mu-opioid receptors, such as methadone, L-α-acetylmethadol (LAAM), and buprenorphine, which can be administered orally and have long half-life [34, 35]. (Last-resort programs based on controlled intravenous administration of heroin are underway in some countries.) These opioid medications, in addition to prevent withdrawal symptoms, reduce the health risks and the criminality associated to street heroin. Furthermore, because of their long half-life and the resulting sustained occupancy of mu-opioid receptor, they produce tolerance to the euphorigenic effect of heroin, thus reducing the risk of relapse. Some detoxification programs utilize, in alternative or in addition to replacement treatments, various medications for the relief of withdrawal symptoms [34, 35].

Detoxification programs based on sustained-release amphetamines have been attempted in cocaine addiction but with very limited success [36-38]. In any case, abstinence from cocaine does not produce a real withdrawal syndrome [39, 40], which represents another major difference between cocaine and heroin addiction.

**Blockade of Drug Reward**

Attempts at blocking the reward effects of addictive drugs have followed three main strategies. The first strategy is based on the use of drugs that block the binding site of the drug and of its active metabolites. Naloxone and naltrexone act as antagonists at the mu opioid receptor, with short and long duration of action, respectively. The short duration of action and poor bioavailability of naloxone restrict the use of this antagonist to the treatment of heroin overdosing. Naltrexone, in contrast, is used for the prevention of relapse in highly motivated individuals. A second strategy originated with buprenorphine, which, being a partial mu-opioid receptor agonist, also acts as a partial antagonist to heroin, hence blocking its rewarding effects [37, 40]. Thus, in maintenance treatment, buprenorphine not only substitutes for heroin but also reduces the rate of relapse. Something akin to a partial agonist at the binding site of cocaine has been identified in vanoxerine, which binds the dopamine transporter with much greater affinity than cocaine while producing only a modest blockade of reuptake [41]. The clinical development of vanorexine has been halted because of cardiotoxicity but other analogs are under investigation. The third approach at blocking drug reward is based on immunotherapy, which, at least conceptually, should work with all addictive drugs [42]. Cocaine vaccines are already tested in human trials and heroin vaccines are undergoing pre-clinical development [43].

**Relapse Prevention**

The theoretical possibility of anti-craving treatments, equally effective for all classes of addictive drugs, is implicit in the unified

models of drug addiction. However, no such common anti-craving therapy has been found yet. Naltrexone has been shown to be moderately effective to reduce craving for heroin and alcohol but not cocaine [44, 45]. As far as dopaminergic agents are concerned, the only effective treatment is represented by disulfiram (which inhibits the conversion of dopamine to norepinephrine). Disulfiram reduces cocaine and alcohol craving (the latter one because of the block of aldehyde dehydrogenase though), but not of heroin craving [46, 47].

### Psychotherapy

Behavioral modification therapy and drug counseling represent the only real overlap in the therapy of heroin and cocaine addiction. The evidence of unique environmental factors in the vulnerability to heroin vs. cocaine addiction (see below) suggest, however, that specific psychotherapies may be developed to target in a more effective manner these two addictions.

### Summary

Decades of experimentation with a variety of pharmacological and psychosocial treatments have not yielded effective therapies for cocaine addiction. This may be due, at least in part, to our incomplete understanding of the factors involved in the vulnerability to cocaine addiction, and in particular in the transition from one stage of the disorder to the next: from the initial, more or less occasional contacts with cocaine to repeated use, and then to compulsive abuse. Vulnerable individuals often exhibit distinct personality traits or psychiatric profiles that are thought to facilitate these transitions [48]. In the following section, we discuss in detail the role of environment as another important, but often neglected, source of variability in the susceptibility to cocaine addiction. In particular, we review data pointing to fundamental differences in the way in which the environment interacts with cocaine relative to heroin and other addictive drugs.

## ENVIRONMENTAL FACTORS IN COCAINE ADDICTION: THE ROLE OF ADVERSE LIFE EVENTS AND OF DRUG CUES

It is well established that the environment plays an important role in human addiction [49-52]. There are many ways the environment can make an individual more vulnerable to develop drug addiction (or to relapse into drug seeking), including drug availability, drug price, presence/absence of alternative non-drug rewards, peer pressure, and adverse life experiences. Even neutral environmental stimuli can acquire, by being associated with drug taking, motivational properties that, in turn, can facilitate drug abuse and trigger relapse. So far, neurobiological research has mostly focussed on the role of adverse life experiences and of drug cues.

### Adverse Life Experiences

There is ample evidence that adverse early life experiences increase the susceptibility to drug abuse [53-59]. Studies in cocaine addicts have shown, for example, that poor child-parent relationships, impair the normal development of personality [60, 61], possibly by producing a dysfunction in the monoaminergic systems of the brain and in HPA axis reactivity [62, 63]. Barck and colleagues found a significant relationship between exposure to early life trauma and vulnerability to current daily hassles in cocaine abusers [64]. Furthermore, events as diverse as sexual abuse/harassment, combat-stress, occupational stress, marriage dissatisfaction, and physical traumas have been linked to the abuse of cocaine and other drugs [65-76]. Sinha and co-workers have shown a relationship between stress-induced corticotropin and cortisol responses, and the amounts of cocaine used per occasion during a 90-day follow-up [77-79]. In another study, using functional brain imaging and script-based imagery to induce stress, the same authors also found abnormal responsiveness to stress in cocaine patients compared to controls, with reduced activation of the anterior cingulate and related circuits, and increased activation of the dorsal striatum/caudate region in correlation with stress-induced cocaine craving [80].

In summary, adverse early life experiences represent important risk factors for cocaine dependence and predict poor treatment outcomes [81]. The nature of this relationship, however, is poorly understood, also because obvious ethical reasons impose severe limitations on the scope of human studies. This has led to the development of animal models (based on the self-administration of drugs through operant conditioning procedure) aimed at investigating the neurobiological underpinnings of the relationship between adverse life experiences and drug addiction. Repeated brief maternal separations in rodents, for example, have been shown to facilitate cocaine self-administration [82] (but see [83]), possibly by facilitating cocaine-induced dopamine overflow in the striatal complex [84, 85]. Similar findings were reported for drugs such as morphine and alcohol [86-89] (but see [90]).

Other animal models concerned with the role early life events in drug addiction are based on the exposure of rodent to "impoverished" vs. "enriched" environments during adolescence. The two-fold rationale for these models is to reproduce the impoverished rearing conditions that are thought to increase vulnerability to drug addiction in humans and to assess the putative protective influence of more stimulating rearing environments. The results of these studies are not consistent, probably because of differences in experimental design, drug delivery system, type of drug, dosage, etc. In some studies, adolescent rats were housed for an extended period of time either individually or in groups of 2-3 per cage and were later single-housed and tested for acquisition of drug self-administration. It was found that single-housed rats exhibit greater susceptibility to the reinforcing effects of cocaine than group-housed rats [91]. Single-housed rats also exhibited a modest facilitation of morphine and heroin self-administration relative to group-housed rats [93-94]. In contrast, other authors reported greater cocaine self-administration in group-housed than in single-housed rats [95-98]. Finally, some authors fond no differences in cocaine or amphetamine self-administration between single- and group-housed rats [99]. In other studies, the group-housing environment consisted of a large chamber containing toys, wheels, and other enrichment items (enriched environment). A series of papers by Bardo and coworkers has shown facilitation of amphetamine self-administration in rats reared in impoverished versus enriched environments [100-102]. Recently, Nader and colleagues (2012) have shown that switching mice from enriched to standard environments increases the rewarding effects of cocaine [103]. Furthermore, rats that had acquired cocaine self-administration behavior and were then exposed to an enriched environment during forced abstinence exhibited reduced susceptibility to relapse into cocaine-seeking when exposed to drug cues or to stressors [104-105], which might be relate to a blunted activation of the brain circuits involved in drug relapse [106-107]. Exposure to an enriched environment during abstinence has also a protective effect versus the incubation of cocaine craving [108], a phenomenon characterized by a time-dependent increase in cocaine-seeking during drug withdrawal in both rodents [109-111] and humans [112]. These findings support the hypothesis that extended exposure to "rich" environmental conditions plays an important role in treatment programs aimed at achieving abstinence.

A number of studies have investigated the effect of chronic food restriction on the self-administration of various drugs, including cocaine, amphetamine, ketamine, and phencyclidine rats or monkeys [113-116]. Food restriction facilitates the acquisition of self-administration behavior for most drugs. Similar findings were obtained by other researchers [117-121]. This phenomenon is so robust that many authors have incorporated food restriction into their self-administration protocols in order to obtain more robust drug self-administration behavior. Interestingly, when food-restricted animals are given again access to food, self-administration behavior declines (114,116,119], indicating that it is the state of the

animals and not the history of deprivation that characterizes this model.

It is not clear what type of mechanism is responsible for the facilitating effect of food restriction on drug self-administration. Conflicting findings on the role of the HPA axis have been reported [123-124]. However, it is reasonable to hypothesize that food restriction produces a non-specific enhancement of the motivational state of the animals. Using a procedure of lateral hypothalamic self-stimulation, Carr and co-workers found that chronic food restriction increases the rewarding effect of various addictive drugs, that is, their ability to lower the threshold for self-stimulation [125]. This phenomenon appears to be mediated by a facilitation of the effects of addictive drugs on dopaminergic transmission. There is in fact some evidence of increased functional up-regulation of D1 and D2 dopaminergic receptors in the striatal complex of food-restricted rats [126, 127]. Furthermore, food restriction has been shown to increase amphetamine-induced expression of Fos (the protein product of the immediate early gene c-*fos*, a marker of neuronal activation) in the terminal regions of the dopaminergic limbic system [125].

Finally, there are animal models concerned with the role of stressors in facilitating drug taking and, most importantly, vulnerability to relapse after abstinence. Relapse is modeled by training animals to self-administer a drug by pressing a lever (or other types of operant behavior) and then withdrawing the drug, which leads to the extinction of lever pressing. The resumption of lever pressing induced by stress, in the absence of drug reinforcement, is taken to indicate relapse to drug seeking [for a review, see 128]. The stressors used in these animal models have various degree of face validity and include: social stress (especially conspecific aggression), electric shock, acute food restriction, tail-pinch, body restraint (immobilization), and the pharmacological stressor yohimbine.

*Social stress.* It has been shown that male rats attacked either by other males or by lactating female rats exhibit greater vulnerability to acquire cocaine self-administration relative to rats engaging in non-aggressive social encounters [129-132]. Interestingly, it appears that social defeat can reduce alcohol self-administration [133-134; but see 135). Although the mechanisms responsible for the facilitating the effects of social stress on cocaine self-administration in the rat are not known, there is some evidence of an involvement of limbic areas such as the prelimbic and infralimbic cortex, NAc, amygdala, and VTA. After repeated exposure to social defeat rats exhibit altered levels of the mRNAs for the transcription factors Fos and zif268 in these brain areas [136-138]. In contrast, it is unlikely that the HPA axis plays more than a permissive role in this phenomenon, as shown by Covington and Miczek [139], who found that after a social encounter both defeated and "victorious" rats exhibited comparable levels of plasma corticosterone and yet stress-induced facilitation of cocaine self-administration was observed only in the former group. There are also reports that subordinated cynomologus monkeys living in a hierarchical social group self-administer more cocaine than dominant monkeys, which has been related to the reduced expression of D2 receptors in the striatal complex [140-141]. Interestingly, social defeat stress promotes escalation of cocaine self-administration but not opiate self-administration.

*Electric shock.* Electrical foot shock and other physical stressors have been reported to facilitate cocaine self-administration and/or to reinstate cocaine-seeking in rodent models of relapse [143-145; but see 146-153]. Similar findings were reported for amphetamine [154], morphine [155], and alcohol [156-158; but see 159-160] self-administration.

*Food restriction*. Acute food restriction can precipitate, in a manner similar to other physical stressors, reinstatement of drug seeking in the rat [151-153], an effect that is attenuated by central infusions of the hormone leptin [150]. Food deprivation-induced relapse, as with other types of stress-induced relapse, appears to depend on the activation of extra-hypothalamic CRH mechanisms because it can be blocked by intracerebroventricular injections of a CRH receptor antagonist (alpha-helical CRH) but not by adrenalectomy, suggesting that corticosterone plays at most a permissive role in this phenomenon [152-153].

*Pharmacological stress*. The α-2 adrenoceptor antagonist yohimbine, which induces stress-like responses in humans and animals, was found to reinstate responding for methamphetamine [161], and for cocaine in squirrel monkeys [162].

The ability of stressors to reinstate cocaine and heroin seeking depends on the activation of extra-hypothalamic corticotropin-releasing hormone (CRH) mechanisms, because this reinstatement is attenuated by intracerebroventricular injections of a CRH receptor antagonist (alpha-helical CRH or d-phenylalanine-CRH) but not by adrenalectomy, suggesting that corticosterone plays at most a permissive role in this phenomenon [163-165]. It has been shown that CRH antagonists act at the terminal of the CRH-containing projections from the central nucleus of the amygdala to the bed nucleus of the stria terminalis [166]. Also adrenergic mechanisms are involved in stress-induced relapse. Blockade of alpha 2-adrenergic receptors has been found to attenuate stress induced cocaine self-administration and stress-induced reinstatement of cocaine- and heroin-seeking in rats, an effect that requires the integrity of the lateral tegmental neurons but not of the locus coeruleus [148, 167].

### Drug Cues

Environmental stimuli paired with drug taking can acquire, through associative learning, the ability to elicit responses related to the drug experience and in particular to precipitate relapse into drug seeking after periods of abstinence. In human addicts, exposure to drug cues can produce withdrawal-like symptoms as well as drug craving [168-169]. The mesotelencephalic dopaminergic system appears to be the main substrate for these effects of drug cues. Cocaine addicts watching a video showing cocaine cues exhibited increased dopaminergic transmission in dorsal striatum [170]. Furthermore, it has been shown that in cocaine addicts "drug words" increase fMRI BOLD signals in the midbrain [171].

More information about the neural underpinnings of cue-induced reinstatement comes from studies conducted using the animal models of relapse described previously. All types of environmental stimuli appear to be effective, because relapse has been observed in response to discrete cues, such lights and/or tones, [172-173], discriminative cues [174-175], and contextual cues [176]. Different types of cues acquire their conditioned stimulus properties by distinct processes. Discrete cues are paired to the manipolandum (e.g., a lever or a hole for nose-poking) and drug infusions during self-administration training. Discriminative cues signal drug availability to animals that are given access to both drug and saline. Contextual cues coincide with the chambers in which the animals were trained to self-administer the drug, and to which they are re-exposed after undergoing an extinction phase in different self-administration chambers. The neural circuitry responsible for the ability of drug cues to induce relapse is very complex [177-179] and include the dopaminergic projections to the nucleus accumbens, the caudate-putamen, and the medial prefrontal cortex [180-186] as well the glutamatergic projections from the prefrontal cortex to the nucleus accumbens [187-188].

## ENVIRONMENTAL FACTORS IN COCAINE ADDICTION: THE SETTING OF DRUG USE

Some environmental factors involved in the initiation and maintenance of cocaine addiction cannot be conceptualized as adverse life experiences or drug cues. In the following we show that the circumstances of drug taking can affect in very different manner cocaine versus heroin use in both humans and laboratory animals.

We decided to compare these two drugs because data from the Vietnam-Era Twin Registry and the Virginia Twin Registry [189, 190] have shown that the environment can exert a substance-specific influence on drug abuse. Yet, very little is known about the nature of these environmental influences. Below we review recent findings that may help account for these epidemiological data.

**Setting Preferences are Drug-specific: Data from Human Studies**

Cocaine addiction and heroin addiction are often considered mere variations of the same disorder. The preference for one drug or another is widely thought to be a function of local availability, street price, lifestyle, and other socio-cultural factors [191, 192]. It has even been suggested that specific drug preferences are simply a matter of chance [193]. By studying the setting of drug taking in human addicts, however, we were able to identify fundamental differences in the setting of cocaine versus heroin use.

Addicts co-abusing heroin and cocaine were recruited, over a period of 2 years, among the outpatients of the addiction clinic Villa Maraini in Rome (Italy), to participate in a retrospective self-report study. The subject enrolled in the study: 1) met DSM-IVR Drug Dependence criteria for cocaine and/or heroin; 2) reported using heroin and/or cocaine (either drug for the Retrospective Reports study, both drugs for the EMA study) at least once a week in the past 3 months; 3) did not meet DSM-IVR criteria for schizophrenia or any other DSM-IV psychotic disorder, history of bipolar disorder, or current major depressive disorder; 4) were not under treatment with antipsychotic medications; 5) did not have other medical conditions that would compromise participation in the study; 6) had a fixed address.

The study was approved by the Ethics Committee of the University Hospital Policlinico Umberto I. All participants personally signed an informed consent form. All participants were legally competent and did not exhibit a compromised ability/capacity to provide informed consent or self-reports as established by the physicians, psychologists, and social workers of Villa Maraini. In no case next of kin, care takers, or guardians provided consent of behalf of the participants.

A total number of 196 addicts participated in the study. The interview was specifically developed to ascertain the physical and social setting in which addicts had taken heroin, cocaine, and heroin plus cocaine ("speedball") in the previous 3 months. The participants were also asked whether the context of drug taking represented a real preference or was the result of constraints related to the route of drug taking. The interview included three batteries of questions for cocaine, heroin, and heroin plus cocaine (speedball), following a stepwise process. Questions about the physical setting included the following:

1) "Where do you usually take cocaine?" (open-ended question)
2) "When you say that you usually take cocaine at ... [depending on the previous answer], you mean always or mostly?"
3) "Where do you prefer taking cocaine? Is it really at ... [depending on the previous answers] or would you take it somewhere else if possible?"

Answers were classified as: always at home, mostly at home, 50/50, mostly outside, always outside. Outside environments were further classified as: street, park, disco, bar, friend's house, friend's car.

Questions about the social setting included the following:

1) "With whom do you usually take cocaine?"
2) "Do you really prefer taking cocaine with …[depending on the previous answers] or would you do otherwise if possible?"

Similar questions were also asked about heroin and speedball taking. The answers were classified as alone, with one companion, with more than two companions. The interviews (10-15 min each) were conducted by a resident physician.

The participants were also asked to provide basic epidemiological and demographic information, including: age, sex, residence, education, employment status, years of cocaine and heroin taking, mean daily dose of cocaine and/or heroin, frequency of cocaine and/or heroin use, use of other drugs, etc. (see Tables **1**).

**Table 1. Demographic and Epidemiological Data of the Participants**

| | **All subjects (N = 196)** | **Heroin/cocaine co-abusers (N = 160)** |
|---|---|---|
| Age (yrs) | 34.9±0.6 | 34.4±0.7 |
| Female/male | 53/143 | 42/118 |
| Yrs of education | 11.1±0.3 | 11.0±0.2 |
| Employed | 65.3% | 58.1% |
| **Heroin abusers** | 95.4% | 100.0% |
| Yrs of heroin use | 15.9±0.9 | 14.5±0.8 |
| Daily dose of street heroin (g) | 1.2±0.8 | 1.2±0.8 |
| Route of heroin taking | | |
| intravenous | 66.8% | 66.9% |
| intranasal | 21.4% | 23.1% |
| inhalation | 10.7% | 9.4% |
| intramuscular | 1.1% | 0.6% |
| Frequency of heroin use | | |
| 1-3 times/week | 15.0% | 5.6% |
| 3-6 times/week | 11.2% | 7.5% |
| daily | 73.8% | 86.9% |
| **Cocaine abusers** | 82.1% | 100% |
| Yrs of cocaine use | 18.9±1.5 | 15.0±0.7 |
| Daily dose of street cocaine (g) | 1.8±0.5 | 1.8±0.5 |
| Route of cocaine taking | | |
| intravenous | 28.6% | 33.8% |
| intranasal | 44.4% | 51.3% |
| inhalation | 13.3% | 15.0% |
| Frequency of cocaine use | | |
| 1-3 times/week | 25.6% | 26.6% |
| 3-6 times/week | 7.8% | 8.9% |
| daily | 65.6% | 64.6% |
| **Other drugs** | | |
| Daily dose of methadone (mg) | 51.7±3.1 | 55.0±2.8 |
| Alcohol abusers | 39.7% | 38.7% |
| Benzodiazepine abusers | 38.8% | 40.0% |
| Cannabis abusers | 30.6% | 31.6% |

The data were compared in two ways, after encoding the subjects' answers for each drug as ordinal data (1 = always at home, 2 = mostly at home, 3 = 50/50, 4 = mostly outside, 5 = always outside). Differences in the setting of cocaine versus heroin taking were assessed using the within-subject Wilcoxon's signed-ranks test. The hypothesis of a significant within-subject switch in setting for heroin versus cocaine taking was tested using the McNemar's test for correlated proportions. In this case, the data for the "always at home" and "mostly at home" conditions were collapsed into the "at home" condition and those for the "always outside the home" and "mostly outside the home" conditions were collapsed into the "outside the home" condition. Given the nature of this test, the co-abusers who answered "50/50" for heroin and/or cocaine taking (N=18) were necessarily excluded from the latter analysis. Obviously, the demographic characteristics of the participants (e.g., age, occupational status, education, etc.) could not represent confounding variables, because every individual was his or her own control. Nevertheless, we examined the relationships between demographic variables and setting preferences using the Fisher's exact probability test and ordered logistic regression (polytomous universal model, PLUM).

Out of the 196 individuals who completed the interview, 160 were active co-abusers. Fig. (**1**) illustrates the setting of cocaine versus heroin use for these individuals (a subset of these data was reported previously [194]). Of all co-abusers, 70.0% preferred to take heroin at home whereas 23.1% preferred to take it outside the home. The results for cocaine were almost exactly the opposite: 22.5% preferred to take it at home vs. about 69.4% outside the home. The Wilcoxon's test indicated that heroin was taken more frequently at home than cocaine ($p < 0.0001$). In about 54% of the subject there was a shift in the setting for heroin vs. cocaine use from the home environment to outside the home environments. The McNemar's test indicated a significant within-subject shift in the setting for cocaine vs. heroin taking ($p < 0.0001$). As illustrated in the bottom panels of Fig. (**1**), the choice on non-home settings differed between heroin and cocaine. Bars and clubs were the preferred settings for cocaine use (57%; Fig. (**1**), left bottom panel) whereas when heroin was taken outside the home it was mostly in the street or friends' car (30% and 16%). Notice that that many individuals indicated more than one non-home environment for drug taking.

Twenty-two subjects reported using speed-ball, with a preference for the home environment over non-home environments (59.1% at home vs. 31.8% outside the home; 9.1% expressed no clear preference).

These differences in physical setting do not appear to be a simple outcome of social setting. When the analysis was limited to the individuals who took the drug in the company of others (Fig. **2**), there were still differences in the setting for cocaine (8.3% at home vs. 83.3% outside the home; 8.3% expressed no clear preference) vs. heroin taking (62.5% at home vs. 33.3% outside the home; 4.2% expressed no clear preference). Furthermore, as illustrated in (Fig. **3**), home was the preferred setting for heroin taking regardless whether the drug was taken in isolation (73% at home vs. 18% outside the home; 9% expressed no clear preference) or in the presence of others (62% at home vs. 33% outside the home; 5% expressed no clear preference).

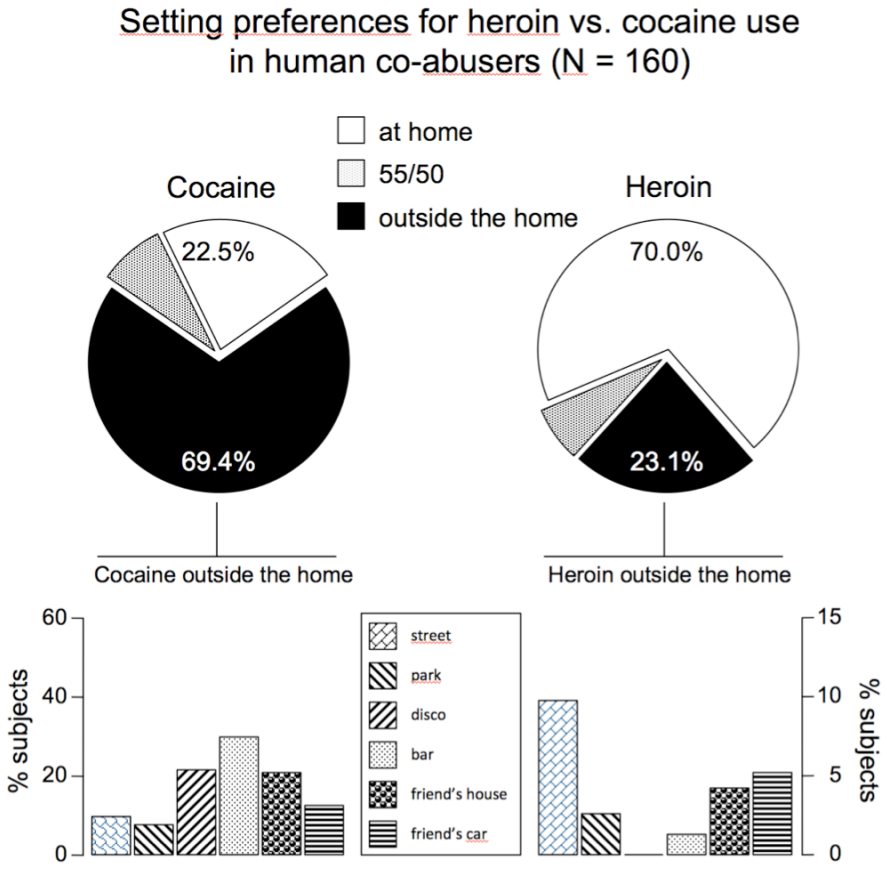


**Fig. (1).** The setting of cocaine versus heroin taking for the individuals abusing both substances independently. To simplify data presentation, the "always at home" and "mostly at home" conditions were collapsed into the "home" condition and those for the "always outside the home" and "mostly outside the home" conditions were collapsed into the "outside the home" condition. The bottom panels detail the choice on non-home settings for heroin and cocaine. Note that many individuals indicated more than one non-home environment for drug taking.

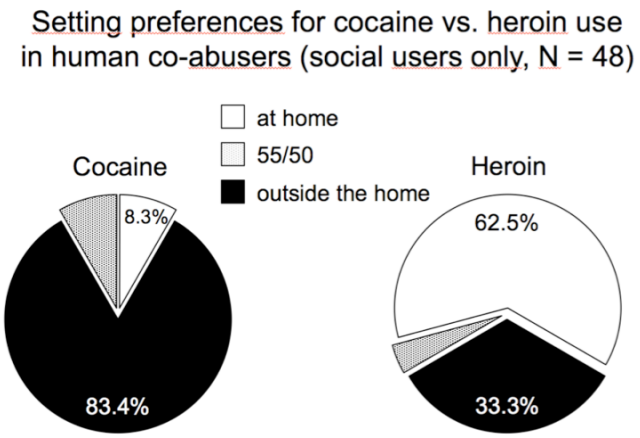


**Fig. (2).** The setting of cocaine versus heroin taking for the individuals who took the drugs in the company of others.

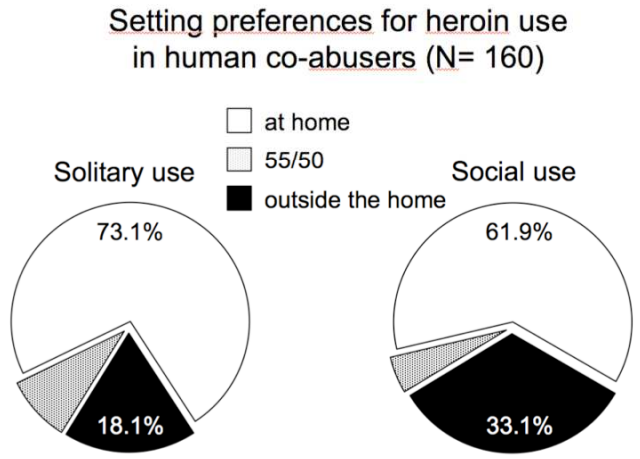


**Fig. (3).** The setting of heroin taking for the individuals who took the drugs either in isolation or in the presence of others.

When the participants were asked whether the context of drug taking represented a real preference or was the result of constraints, they confirmed that they took the drug(s) in the preferred setting. In particular, it is important to note that the route of administration did not affect setting preferences, as similar results were obtained when the analysis was limited to the individuals who used the same route of administration for both drugs, that is, who injected or snorted both cocaine and heroin separately (Fig. **4**).

Finally, none of the socio-demographic variables illustrated in (Table **1**) had any significant influence on setting preferences for either cocaine or heroin, as indicated by analysis with the Fisher's exact probability test and with ordered logistic regression.

Three major findings are reported here. First, addicts co-abusing heroin and cocaine exhibit differential setting preferences for heroin vs. cocaine use. Second, setting preferences were independent of the route of dug taking. Third, setting preferences were not a mere consequence of the preference for one social context or the other. The within-subject design of our study makes the findings especially compelling, because the difference in preferred settings for heroin vs. cocaine use cannot be attributed to differences in drug availability, peer influence, or other socio-demo-graphic factors.

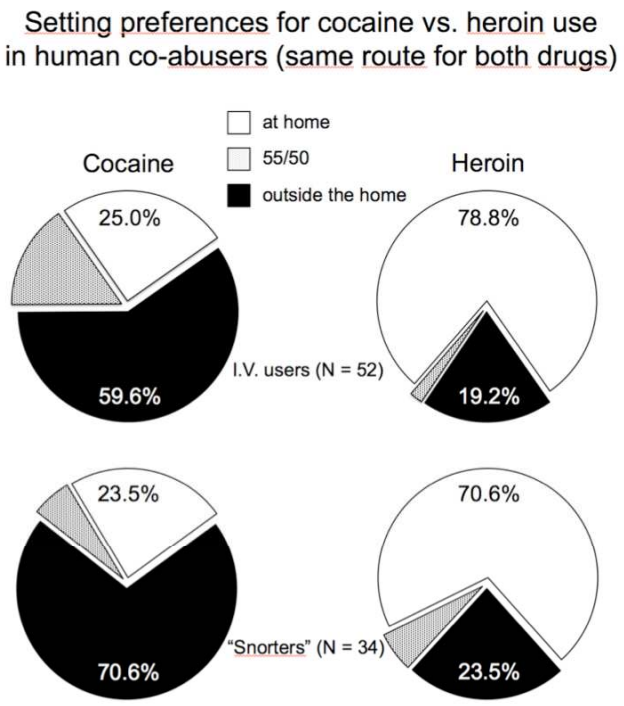


**Fig. (4).** The setting of cocaine versus heroin taking for the individuals who used the same route of administration for both drugs, that is, who injected or snorted both cocaine and heroin in distinct occasions (i.e., not combined as "speedball").

What type of explanation can account for the interaction between drug and setting described here? We have argued that the environment influences the reward effects of drugs as a result of the appraisal of drug effects in relation to the surrounding stimuli [6; 194, 195]. Each addictive drug produces a distinctive constellation of desired and undesired effects, which may or may not partly overlap with those of other drugs. Some of these effects may be largely "indifferent" to environmental context whereas other effects would be more appropriate (or less inappropriate) to certain settings. The activating, performance-enhancing effects of cocaine and amphetamine, for example, would be experienced as more suitable to an exciting, relatively novel environment than to a home environment. In contrast, the sedative, inward-looking effects of heroin would be experienced as more appropriate to a safe, non-challenging, home environment. That is, we hypothesize that the setting might affect drug choice by providing an ecological backdrop against which drug effects are appraised as more or less "adaptive". It is important to emphasize that emotional appraisal does not necessarily entails the conscious evaluation of stimuli [195-196]. That is, the fact that heroin is preferentially taken at home should not be seen as the mere expression of an intentional decision to take a depressant drug in a place where one can lie down and an activating drug where one can move around. The results of studies conducted in rats, and reviewed below suggest that it is the setting that endows drug effects with emotional valence, rather than the other way round.

### Drug Preferences are Setting-specific: Data from Animal Studies

For obvious reasons, it is difficult to manipulate the setting of drug taking in real-world addiction. In contrast, this manipulation is perfectly feasible in the rat. In a series of studies, we trained rats to self-administer heroin or cocaine under two deceptively similar

conditions. Some rats were transferred to self-administration chambers immediately before experimental sessions (Non Resident rats). Other rats were kept in the self-administration chambers at all times (Resident rats). Thus, the physical characteristics of the self-administration environment for Resident vs. Non-Resident rats were virtually identical, all differences being purely "psychological" and resting on the appraisal of the context by the rat. We found that cocaine self-administration was greater and more rewarding in Non Resident rats than in Resident rats [197-198]. In contrast, heroin self-administration was greater and more rewarding in Resident rats than in Non Resident rats. As illustrated in (Fig. **5**), Resident and Non Resident rats also exhibited distinct preferences for cocaine or heroin. In this experiment, rats with double-lumen catheters were first trained to self-administer both cocaine and heroin on alternate days and were then repeatedly given the opportunity to self-administer cocaine or heroin within the same session. Under these conditions, most Resident rats preferred heroin over cocaine (as indicated by bootstrapping analysis), whereas most Non Resident rats preferred cocaine over heroin [199]. Furthermore, preliminary data from our laboratory suggest that Resident and Non Resident rats trained to self-administer, on alternate days, heroin and cocaine exhibit differential propensity to reinstate heroin vs. cocaine seeking after extinction of the drug-reinforced responding. A small dose of heroin (heroin priming) had a stronger effect on reinstatement in the Resident rats than in the Non Resident rats. In contrast, cocaine priming had a stronger effect on reinstatement in the Non-Resident rats than in the Resident rats. Interestingly, experiments based on drug-discrimination procedures suggest that opiates and psychostimulants produce interoceptive cues of different strength in Resident rats than in Non Resident rats [199-200]. Non Resident rats discriminated amphetamine or cocaine from saline more readily than Resident rats, whereas Resident rats discriminated heroin from saline more readily than Non Resident rats. Thus, the setting of drug exposure modulates, in opposite directions both the rewarding and the interoceptive effects of opiates versus psychostimulants in the laboratory rat.

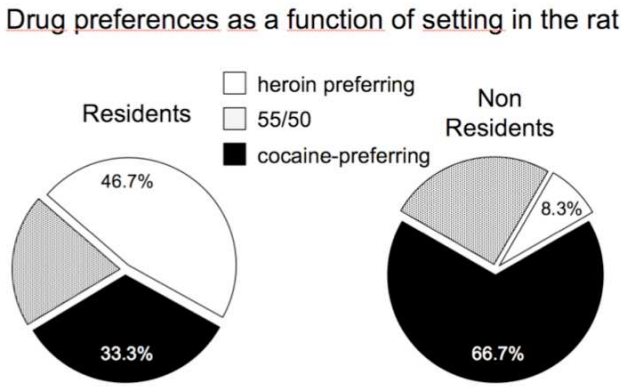


**Fig. (5).** Drug choice as a function of the setting of drug taking in rats (data from [194]).

The neurobiological mechanisms underlying the effects of setting on cocaine vs. heroin self-administration in the rat are unknown. Earlier studies conducted with intraperitonal injections of these two drugs have shown that the setting can powerfully alter, both quantitatively and qualitatively, their ability to induce the expression of the immediate early gene c-fos (or of the transcript protein Fos) in the cortex, in the striatal complex, and in the amygdala [201-209]. In particular, it was found that when cocaine was administered under non-resident conditions, it increased Fos mRNA expression in the neurons of both the direct (striatonigral) and indirect (striatopallidal) projection pathways of the striatum. In contrast, when given at home, cocaine increased c-fos expression only in the neurons of the direct pathway [205]. More recent *in situ* hybridizaton experiments, in which much smaller doses (i.e., the same unit doses used in self-administration studies) were administered intravenously, confirmed that the context modulates in very different manner cocaine- vs. heroin-induced c-*fos* expression in the dorsal caudate and other brain areas [198].

The data from the animal studies summarized above not only are in agreement with the human data discussed previously, but also shed some light on the nature of the interaction between drug and setting in human addicts. Contrary to humans, it would be difficult to envisage any degree of mental planning in the case of our rats, not only because attributing conscious planning to rats would be questionable at best. Resident rats, for example, did not have the choice between different settings but simply adapted their behavior to the context by taking less cocaine and more heroin than the Non Resident rats. The results of the in situ hybridization studies further confirm that the setting can modify in a substance-specific manner the effects of addictive drugs on brain and behavior.

## CONCLUSIONS AND FUTURE DIRECTION

It has been known for many years that environmental contexts or places in which drugs are taken play an important role in human addiction. We reviewed here recent findings showing that the setting in which cocaine is taken can powerfully influence the rewarding effects of this drug. Most important, we report here original data indicating that there are major differences between heroin and cocaine use in both real-life addicts and in rats given access to both drugs. Other pre-clinical and clinical findings, including the lack of pharmacological treatments effective for both cocaine and heroin addiction support the notion that much is to be gained by taking into account the substance-specific aspects of drug addiction [6, 194, 210, 211]. In particular, these differences may have important implications at a therapeutic level, suggesting, for example, that cognitive-behavioral approaches should be tailored so as to allow the addict to anticipate, and cope with, the risks associated in a substance-specific manner to the various environmental settings of drug use. In a recent study, for example, a memory retrieval-extinction procedure has been used to prevent drug craving and relapse in a sample of heroin addicts [212]. A similar approach may be used to address the risks associated to exposure to specific settings of drug use. Ecological momentary intervention (EMI) approaches can also be used to develop dynamically and individually tailored intervention [213, 214], which, by being ecologically sensitive, may provide real-time support in the real world.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

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