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Have we reproduced Rat Park? Conceptual but not direct replication of the protective effects of social and environmental enrichment in addiction

Shaun Yon-Seng Khoo

Department of Pharmacology and Physiology
Faculty of Medicine
Université de Montréal
Montreal, Quebec, Canada
shaun.khoo@umontreal.ca
https://orcid.org/0000-0002-0972-3788

Abstract

The Rat Park studies are classic experiments in addiction neuroscience, yet they have not been successfully replicated directly and several serious methodological criticisms have been raised. However, the conceptual reproducibility of the Rat Park studies is supported by both contemporaneous and subsequent research. Contemporaneous research on social and environmental enrichment frequently found social isolation rendered rats less sensitive to the effects of drugs of abuse. The Rat Park studies therefore confirmed the importance of social and environmental enrichment and extended this literature to suggest that enrichment reduced opioid consumption. Subsequent studies have also demonstrated social and environmental enrichment reduces drug consumption. However, there are also several papers reporting no effects of enrichment (or 'negative' results) and caveats from studies that show genes, age, sex and drug of abuse are all important parameters. While the Rat Park studies did not use methods that are reliable by current standards, enrichment has been shown to reliably reduce opioid consumption and this effect can generalise to other drugs of abuse.

Keywords: Rat Park, Addiction, Environment, Social, Enrichment, Housing

Introduction

The Rat Park studies are now considered classic experiments in addiction neuroscience (1). In these studies by Alexander and colleagues, male and female rats were housed individually in bare cages or socially in a mixed-sex colony with a variety of physical compartments and enrichment opportunities (2). A morphine solution was available on a variety of access schedules, including 7 h/day, 57 days of near constant forced access and intermittent access (24 h on, 24 h off), and consumption was measured individually by video-monitoring of the morphine access station (3). Overall, these studies showed that social isolation induced higher levels of morphine consumption in rats (2), that early isolation had long-lasting effects (4), and that isolated female rats drank more than isolated male rats (5).

The key conclusions from these studies were that social and environmental factors are important factors in drug abuse. Alexander and Hadaway argued that these results supported the idea that drug use, specifically opioid use, occurred in order to cope with chronic distress rather than being driven by the intrinsic neuropharmacological effects of opioids (6). They reasoned that by providing animals with social and environmental enrichment, they were reducing their level of chronic distress and therefore motivation to consume morphine. Alternatively, they suggested that the pharmacological effects of morphine might impair an animal's ability to engage in reinforcing social activities in the colony environment (6).

The Rat Park papers are now 40 years old, yet ongoing media interest and their legacy in the

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field continue to support a high replication value for these experiments (7). As several reviews have noted (1, 8), an attempted replication of the studies was reported in 1996 and did not show the same effects (9). However, it is not clear that further direct replication attempts are desirable as the original studies had several methodological flaws including lost data, animals dying during experiments and confounding variables such as intake modality.

The reproducibility of the Rat Park experiments can be conceptualised in multiple ways. Some argue that direct replication, using methods that are as close as possible to the original study, is the ideal way to verify the reliability of an effect (10). Others argue that it is more important to replicate the manipulation of the underlying theoretical variables, in other words, to conduct conceptual replication (11). Similarly, Nosek and Errington recently argued that a replication is any study where the outcome would provide evidence that increases or decreases confidence in the original claims (12). In light of the unsuccessful direct replication of the Rat Park experiments and the methodological issues with the original studies (9), a successful direct replication of the experiments has neither occurred nor should further attempts be made.

In the case of the Rat Park studies, the better approach is to examine its underlying variables of social and environmental enrichment and to consider whether subsequent studies have increased or decreased confidence in their protective effects against drug abuse, specifically opioid abuse. These studies have begun to delineate and more precisely examine the role of the key factors identified in the Rat Park studies, including social housing, environmental enrichment and reward choice. Together, these findings show that while direct replication of Rat Park is no longer desirable, the concept that social and environmental enrichment reduces opioid consumption is highly reproducible and extends to other drugs.

Direct Replication and Methodological Considerations

Direct replication of the Rat Park studies is no longer desirable due to both methodological problems with the original studies and theoretical advances in the subsequent decades. The original studies suffered from equipment failures that resulted in the loss of several days of data and four female rats died during the forced consumption period, when only morphine solutions were available (2). A fifth female rat died during the abstinence phase of the experiment, where a choice between morphine and water was available on test days but only water was available for 5 weeks. While the null result in the 1996 direct replication attempt was mostly attributed to genetic or strain differences (1, 9), another possibility is that complete measurements and improved animal health reduced the potential for false positives. Nonetheless, subsequent studies have supported the main conclusions of the Rat Park studies (as discussed below).

The provision of morphine for oral consumption also lacks validity as an addiction model, since human opioid abusers do not typically drink solutions of morphine. Morphine's bitter taste makes it unpalatable to rats and suppresses their consumption (13). While the first Rat Park study provided an unsweetened solution of morphine in tap water, multiple animals died (2) and the two subsequent papers and 1996 replication attempt provided morphine in a sucrose solution (4, 5, 9). This further complicates interpretation of the rats' behaviour since it is difficult to definitively attribute the results to either sucrose preference or preference for the pharmacological effects of morphine.

Even the measurement of the morphine solution consumption is confounded. For socially isolated rats, morphine was simply available via water bottles, similar to contemporary 2-bottle free choice paradigms (2). However, to correctly attribute the morphine consumption of each individual colony rat, these rats were marked with coloured dye and had to enter a specialised

area that triggered video recording. Rats had to perform light beam breaks above the well to have a drop of fluid dispensed for them or, in other words, perform an operant response for the reinforcer (2, 3). The measurements for the colony rats were therefore fundamentally different to the measurements for the socially isolated rats.

The interpretation of the Rat Parks studies is also confounded by the multiple and potentially interacting variables. Colony rats had access to both same and opposite-sex conspecifics. They had access to more space, which was compartmentalised and contained environmental enrichment. As discussed above, they obtained morphine in a different way to socially isolated rats (2). While most of these social and environmental variables are what was thought to contribute to the observed differences in morphine consumption, the potential interactions confound precise attribution of these differences to their underlying causes.

Progress in the neuroscience of addiction now demands a much higher level of precision from scientists than was possible in the 1970s and 1980s. Contemporary scientists would rightly demand that further studies use a method of administration that better translates to human substance use disorders, equate approaches for drug consumption and isolate variables such as social housing and enrichment of the physical environment. These advances render an attempted direct replication of the Rat Park experiments no longer justifiable.

Historical Context of the Rat Park Studies

Direct replication of the Rat Park experiments may no longer be justifiable, but within its historical context it made important conceptual progress from previous studies. If replication is predicated on the theoretical concepts being manipulated (11) or a study's ability to affect confidence in previous findings (12), then how well the conclusions of the Rat Park experiments fit in with its contemporaneous studies is indicative of its reproducibility.

The Rat Park papers published between 1978 and 1981 (2, 4, 5), were consistent with several contemporaneous studies that showed socially and environmentally enriched housing altered responses to drugs of abuse. In 1976, Hill and Powell reported that individually housed rats drank less cocaine solution than group-housed rats (14). While this might, at first, appear to contradict the Rat Park study, it is important to note that Hill and Powell's group-housed rats were transferred to individual housing in order to measure cocaine consumption. It is therefore plausible that the acute social deprivation experienced by the previously group-housed rats drove their increased cocaine consumption.

Hill and Powell's study directly contrasts with the results of the Rat Park studies because they showed no change in consumption of a morphine solution between socially housed and isolated animals (14). Hill and Powell's morphine solution was 0.5 mg/mL morphine sulphate, similar to the 0.5 mg/mL morphine hydrochloride used in the first Rat Park paper (2, 14), but they reported levels of morphine consumption around 1 mg/kg or less in all animals. While this was comparable to the socially housed animals in the Rat Park experiments, the isolated animals in the Rat Park experiments consumed up to 20 mg/kg. As noted by Alexander and colleagues in 1978, taste perception is a likely contributor to these effects (2) and it is plausible that differences in taste between the sulphate and hydrochloride salts or between taste perception in Charles River Canada Wistar rats used in Rat Park and the Wistar rats bred by Hill and Powell explain these differential findings (9, 14).

Colony-based housing was also used in several prior addiction studies, examining the sensitivity of animals in various conditions to stimulants and opioids. At the 1966 meeting of the Association for the Study of Animal Behaviour studies were presented on how the exploratory behaviour of environmentally enriched rats was initially more sensitive to acute injections of an amphetamine-barbiturate

mixture than non-enriched rats, but that this contrast was reversed in a later test (15). Contemporaneous work also examined the effect of acute amphetamine administration on aggression in mice housed in groups of up to 10 (16). Several studies comparing sensitivity and consumption in rodents housed in large groups to socially isolated animals were also performed for central nervous system depressants such as morphine. A study published in 1970 demonstrated that rats housed in a colony with 12 rats per cage were more sensitive to acute experimenter-administered morphine injections, as measured by a Y-maze (17). These results in rats replicated findings in mice that social housing was associated with greater sensitivity to depressants than individual housing (18). Additionally, Hill and Powell cite a 1973 paper that did not find any effect of an enriched environment relative to an impoverished environment on alcohol consumption in rats (19).

The Rat Park studies were therefore not the first papers to examine the effect of social housing on drugs of abuse. Nor were they the first papers to show an effect of socially and environmentally enriched housing conditions on drug consumption, since Hill and Powell previously reported effects on cocaine consumption (14). While the 1996 replication attempt might be more consistent with the 1976 Hill and Powell studies, as far as null results for morphine consumption are concerned (9, 14), the Rat Park studies were neither a completely novel approach in terms of comparing social isolation to enriched housing conditions, nor were they unusual in terms of finding an effect of differential housing on consumption or sensitivity to drugs of abuse. If replication is defined conceptually or is based on influencing confidence in previous findings (11, 12), the Rat Park studies themselves replicated previous findings which had demonstrated the importance of social and environmental conditions, but extended those findings by suggesting that enrichment would be protective against opioids.

Conceptual Replication and Generalisability

In the decades since the Rat Park experiments, numerous studies have shown that the effects of social and environmental enrichment can alter behavioural responses to drugs. These studies have used very different methods to examine the underlying variables of social and environmental enrichment, and so can be considered as either conceptual replications (11) or, where studies reporting no effect of social or environmental enrichment ('negative' results) do not decrease confidence in the conclusions of the Rat Park studies, as generalisability tests (12). Conditioned place preference studies show that housing conditions, particularly those in place from an early age, can alter sensitivity to the rewarding effects of drugs of abuse. For opioids, stronger conditioned place preference is reported in socially or environmentally enriched animals. These effects also generalise to stimulants, but there are several negative results. However, altering the rewarding properties of a drug does not necessarily indicate how animals will behave when given opportunities to self-administer drugs. Intravenous self-administration studies provide evidence that social and environmental enrichment reduce opioid consumption. For stimulant drugs, the evidence is stronger for a protective effect of environmental enrichment rather than social enrichment. Finally, novel choice paradigms have recently provided strong evidence that animals prefer non-drug consummatory and social rewards over drug rewards.

Conditioned Place Preference: Opioids

Studies of conditioned place preference have consistently shown that group housing or environmental enrichment make animals more sensitive to the rewarding effects of opioids (20). Rats that are socially isolated from weaning require higher doses of heroin in order to acquire conditioned place preference than quad-housed rats (21). Similarly, rats isolated after a more mature age (>17 weeks)

did not show differential conditioned place preference, while rats isolated from weaning appear to be less sensitive to heroin place preference (22). Consistent with these findings, environmental enrichment of group-housed non-littermate mice prevented conditioned place preference for heroin (23).

Animal studies also show that housing conditions alter sensitivity to the aversive effects of high dose opioids. In these studies, experimenters administer a high dose of drug in association with the availability of a sweet solution, such as saccharin. By repeatedly pairing the aversive experience of a high opioid dose to saccharin availability, animals acquire an aversion to the saccharin. Studies from separate groups have shown that socially isolated rats are less sensitive to morphine-conditioned taste aversion to saccharin (24, 25). Together, with the place preference studies, these demonstrate a reduced sensitivity to the mood-altering effects of opioids in socially isolated animals. Moreover, they suggest that housing conditions are likely to alter voluntary self-administration even if they do not conclusively indicate the direction of the effect.

Conditioned Place Preference: Stimulants

Conditioned place preference studies are more equivocal for stimulant drugs than for opioids. An earlier study found socially isolated rats were insensitive to cocaine place preference while rats housed in groups of four acquired cocaine place preference (26). Not all studies on social and environmental enrichment have found significant effects on place preference for stimulants (20), for example, wheel running had no effect on cocaine place preference (27). However, more recent studies tend to report that social and environmental enrichment reduced cocaine place preference (28, 29) and cocaine-induced expression of neural activity markers (30). Mice housed in groups of 10 in an enriched multi-storey cage showed less cocaine place preference than mice housed in groups of 2-3 in standard polycarbonate cages (31). Enrichment can also reduce reinstatement of cocaine place preference even when only introduced after animals had already acquired the association (32, 33).

Studies of amphetamine-conditioned place preference are even more equivocal, as suggested by a 1995 meta-analysis (20). One study that had reported effects for cocaine found no effect on amphetamine place preference (26). However, other studies have found social housing can reduce amphetamine place preference (34). This effect may be related to the relative maturity of the animals because pair-housed adolescent, but not adult rats, were shown to acquire amphetamine place preference (35). While less studied than both amphetamine and cocaine, methamphetamine place preference appears unaffected by environmental enrichment (36). These mixed results suggest that the specific drug, even within drug-classes, may influence whether social and environmental enrichment alters place preference.

Conditioned place preference paradigms provide evidence that social and environmental conditions can alter the rewarding properties of drugs, but this does not necessarily indicate whether these effects are protective against addiction. For opioids, social and environmental enrichment was associated with increased drug reward. In contrast, studies with stimulant drugs have shown both increases and decreases in conditioned place preference under conditions of social and environmental enrichment. While these studies demonstrate that reward value is sensitive to social and environmental housing conditions, they do not necessarily indicate whether these effects are protective against addiction. In theory, increased reward value should increase motivation. On the other hand, satiety may be reached more quickly or increased sensitivity to the drug's intoxicating effects may alter the expression of place preference. Therefore, the results of these studies must be interpreted alongside voluntary self-administration paradigms.

Intravenous Self-Administration: Opioids

Intravenous opioid self-administration studies have demonstrated that social and environmental enrichment have protective effects, reducing voluntary opioid consumption. A 1989 paper showed housing rats in large groups (10 rats/cage) resulted in lower heroin self-administration (37). More recently, a 2017 paper examined the effects of housing conditions on self-administration of the synthetic opioid remifentanil (38). Animals were randomly allocated to three conditions: socially isolated in a small cage with a grid floor, standard pair-housing in a bare regular cage with bedding or enriched housing in a large cage in groups of 5-8 with several objects. Rats kept in enriched group housing still acquired operant responding for intravenous remifentanil, but consumed less than their counterparts housed under standard or socially isolated conditions (38). The protective effects of environmental enrichment were further demonstrated in a 2018 study where enriched rats had access to a variety of objects and a running wheel. Animals in the enriched housing condition acquired a similar level of heroin self-administration, but showed reduced motivation to consume heroin and relapse propensity in progressive ratio and reinstatement tests (39). These studies conceptually replicate the key findings of the Rat Park studies and Hill and Powell's experiments, demonstrating that across different opioid reinforcers and research groups, social and environmental enrichment reduce addiction-like behaviours in animals.

Intravenous Self-administration: Stimulants

Intravenous stimulant self-administration studies mirror conditioned place preference studies in providing more equivocal evidence for the effects of social and environmental enrichment on consumption. For example, there does not appear to be strong evidence of a protective effect of social housing alone on stimulant consumption. In one study, socially isolated rats had higher mean cocaine consumption than group-housed animals, but the difference was not statistically significant (37). In another study, socially isolated rats had similar cocaine consumption to group-housed animals, except at a low dose of cocaine, where isolated rats consumed more (40). These effects may also rely on specific genotypes or strains (41) and may be sex-based as one study found female but not male rats escalated intake in response to social isolation (42). Amphetamine self-administration was also unaffected by social housing conditions (43).

Environmental enrichment, on the other hand, appears to be of greater benefit. Group-housed rats in an enriched environment were found to self-administer less cocaine than isolated rats in a non-enriched environment (44). A combination of social and environmental enrichment has been shown to facilitate extinction (45) and attenuate cue-induced reinstatement behaviour in rats (46). A separate study found similar effects on cue and stress-induced reinstatement, but held the social groupings constant across environmentally enriched and standard housing conditions (47). These results suggest that, while evidence for the protective effects of social housing alone are weak, there is stronger evidence for the protective effect of environmental enrichment, even in absence of social housing.

Choice Studies

Recently, behavioural neuroscientists have developed novel paradigms for studying the social and environmental factors underlying drug self-administration in animals. When given an alternative to drugs, animals in self-administration paradigms frequently choose non-drug alternatives. For example, if rats are given a choice between a saccharin reward and cocaine, most rats will choose the saccharin reward (48). This finding has been replicated for multiple drugs of abuse, including heroin and nicotine (49-52).

Researchers are also pioneering methods of providing social rewards as alternatives to animals. While it has been known for some time that social defeat can promote

drug-taking (53), neuroscientists have now begun to offer animals a choice between drug use and social interaction (54). These experiments have shown that the availability of a social choice induces voluntary abstinence in a majority of animals from consumption of both methamphetamine and heroin (55-57). These new experiments demonstrate that drugs of abuse are not preferred by animals when there are alternative consummatory or social rewards available. They therefore support Alexander and Hadaway's suggestion that reduced morphine consumption in socially housed animals in the Rat Park experiments could be caused by the fact that consumption interfered with social functions (6). These studies therefore increase confidence in the idea that social and environmental enrichment can have protective effects against drug addiction.

Conclusions

It has now been more than 40 years since the Rat Park studies took place. In that time, these simple experiments have been critiqued and analysed repeatedly, helping to inspire generations of scientists to consider the social and environmental factors underlying addiction (1). While many of these studies have reproduced the protective effects of social and environmental enrichment, it is important to note the literature contains several negative findings and caveats which suggest that while social and environmental enrichment is generally protective, this is not always the case. Genotypes, strains, age and sex all play a role in promoting or protecting against drug addiction, and may interact with social and environmental interventions. This is well-illustrated by contemporary choice studies, which show that while the availability of a non-drug or social reward can induce voluntary abstinence, there remain a minority of animals that prefer the drug. Moreover, the drug of abuse still plays a role, with greater consistency of findings for opioids than for stimulant drugs.

The Rat Park studies are far more reproducible conceptually than methodologically. For researchers who believe that direct replication is essential for determining a study's reliability (10), the lack of a successful direct replication and flaws in the design and execution of the original studies lead to the conclusion that the Rat Park studies are not reproducible.

A more charitable view of the Rat Park studies is derived from characterising replication based on the theoretical concepts and variables involved (11, 12). Taking this view, the Rat Park experiments become one of several early studies that provided evidence of the importance of social and environmental enrichment. Subsequent studies suggest that social and environmental enrichment reduce consumption of drugs of abuse. While the failure to directly replicate (9) should be taken into account and decreases confidence in the reliability of the conclusions of the Rat Park studies (12), the weight of the literature provides confidence that the protective effects of social and environmental enrichment are reproducible.

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