

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

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Reviewer's comments

Reviewer A:

The author interestingly set up rationally creative comparisons around some classical works, conceptualized as the “Rat Park papers”, to introduce the audience to an overview of how social interaction or environmental enrichment may or may not be important for the pattern of drug addiction. In general the work is well written and of great interest for both the scientific and also lay community, since addiction-related issues represent a social burden worldwide. I dealt with just a few comments to make the text clearer.

Not the First Rodent Colony

In a sequence of the work’s description, the author showed that environmentally enriched rats and mice housed in groups, or rats housed in a colony, were more sensitive to amphetamine-barbiturate, amphetamine or morphine, respectively. In the context of drug addiction this can be ambiguous, especially if you are talking about stimulants which can trigger sensitization and a boosting of behavioral and neuroendocrine effects even after repeating the same drug dosage. Or is the description of sensitivity related only to an increased drug consumption? Please clarify what it means to be more sensitive to drug injections by detailing it.

Response: Psychomotor sensitization requires repeated injections to trigger sensitization, but the studies being surveyed in this section used acute administration procedures. To clarify, I have noted in this section that administration was “acute” and provided more details about the measurements – i.e. with reference to “exploratory behaviour” or to say that the study measures “the acute effect of amphetamine on aggression in mice”.

Decades of Conceptual Replication

Opioids

First the author states “Studies of conditioned place preference have consistently shown that group housing or environmental enrichment makes animals less sensitive to the rewarding effects of opioids”. But then all the works describe that isolated animals require a higher dose of the drug or cannot even acquire a preference for a conditioned place. Also, isolated animals were less sensitive to morphine-conditioned taste aversion. By the end the author concludes “Together, with the place preference studies, these demonstrate a reduced sensitivity to the mood-altering effects of opioids in socially isolated animals”. So, opposite to what was said at

first, isolation seems to make the animals less sensitive to the rewarding effects of opioids. Please, make these inconsistencies clearer and also clarify the introduction statement properly.

Response: Thank you to the reviewer for catching this inconsistency. I had mistakenly written “less” instead of “more” in this sentence. The Bardo et al. (1995) paper cited here shows significantly higher average effect sizes for conditioned place preference in group-housed (0.46 ± 0.05) than individually housed (0.28 ± 0.07) rats. I have corrected this error and rewritten the introductory paragraph for this section.

It seems that actually all the works addressing the drug’s effect on place preference found the isolated animals less sensitive to the rewarding effects of opioids. Otherwise, in the self-administration/operant paradigms the group housing and environmental enrichment were protective of the drug’s effect. Wouldn’t the difference between being protective or not be a matter of the paradigm used (operant/non-operant or self/non-self drug administration)?

Response: This is a fair point. To address this I have reorganised the section on conceptual replication to follow the experimental design – conditioned place preference, self-administration, and choice models. Prior to the discussion of intravenous self-administration, I have added a paragraph to discuss how altered reward sensitivity demonstrates that social and environmental enrichment are important factors, but need to be interpreted alongside the self-administration paradigms. At first glance, increasing reward sensitivity should increase motivation for the drug. However, there are also other possibilities, like rats becoming sated more quickly or sensitivity to the drug’s other effects altering expression of place preference. While the place preference studies are valuable, the self-administration studies and choice studies demonstrate the direction of the effect more clearly.

Reviewer B:

First of all, I think that the author has chosen an interesting and important topic for their review: the Rat Park studies remain a group of addiction-related reports that have had a surprising amount of air space, both in public conversations and within the field, even decades after their publication. Due to this, and to the clear faults/problems in the original papers also pointed out by the author, I believe a reproducibility point of view on the Rat Park studies is something that deserves a proper, critical review.

However, I am not convinced that this can be achieved with the text at hand. My number one problem with the manuscript is that it is difficult to grasp the main message of the text.

As the text currently reads, the main message seems to be along the lines that the Rat Park studies should not even be considered for a proper replication study due to their flaws, but that conceptual replication, i.e. replicating the main finding with different kinds of paradigms and settings, should be the way to go. Further, this has actually already been done several times, but with plenty of contradicting results in the literature.

Since the journal is about reproducibility, I would like to see more in-depth analysis of these contradicting reports – have they been able to control all the factors in a way that the end result can be considered more valid than the original Rat Park experiment, for example – alongside some consideration of what the main finding or message of the original Rat Park papers really is: is it the actual direction of the difference between the study groups (i.e. the protective effect) or is it the conclusion that the authors actually make themselves in their original paper, that the environment and the sex of the studied subjects are actually important variables. As these are

very different things, I would like to see more clear wording of the “concept” which this piece is discussing replicating, and maybe why it is more important than the other one.

Response: I have expanded the introduction to be more clear with respect to the “concept” of the Rat Park studies – that it is the protective effect of social and environmental enrichment, particularly with respect to opioids. While the authors do not explicitly make this argument in the empirical papers, Alexander and Hadaway (1982) make these arguments more explicit.

Also, if there is a plethora of literature describing negative results, as there seems to be based on the research cited by the author, can the protective effects of the environment then be said to be successfully replicated, as the author implies?

Response: Negative results are primarily reported for stimulant drugs of abuse. For Nosek and Errington (2020), this might be considered more of a generalisability test than a conceptual replication. I have added some context on the conceptualisation of replication in the introduction and restructured the paper around these ideas.

Related to the above mentioned comment, since the main message of the text is not solid enough, the last sentence of the manuscript – stating that it is still important to study the environment and other varying conditions – could be considered to summarize the take home message of the text. If so, I have trouble finding the novelty of this piece, as the main point is almost identical, for example, to the one in the Gage and Sumnall 2019 review in Addiction, also cited by the author.

Response: Gage and Sumnall’s review is not as in depth or as focused on the reproducibility of Rat Park. It considers only the Rat Park studies and a small selection of contemporaneous works. It does not consider whether the subsequent literature has shown that social and environmental conditions have been reliably shown to be important (protective) factors in addiction. I have reworded the conclusion to provide a stronger discussion of the reproducibility of Rat Park.

There are also a group of smaller things I wish to point out:

There are also terms that are used, in my mind, unconventionally, especially the word ecological validity, which is usually used to mean the extent to which the findings of a certain study can be generalized to the more general population, usually from human laboratory experiments to “real life”. As rodent studies cannot be generalized to human addiction patients in any case, the correct word should be translation, or some variant of this.

Response: I have not been able to verify that “ecological validity” is defined as within-species only. Nonetheless, I have removed the word “ecological” from these sentences.

Ecological validity is also at the centre of another small point, and that is a small disagreement I seem to have with the author on the main flaws of the original Rat Park papers, as the different administration route, or the intake modality (orally with rats, i.v. injections in humans), might not really be that big of a problem. It is of course true that the translatability of the findings can be questioned on this basis, but it should also be noted that overly human-centric experimental design is considered to be one of the causes of the reproducibility crisis in animal behavioural studies (see e.g. Kafkafi et al. Neurosci Biobehav R, 87, 2018). Therefore orally administered morphine could actually be more ecologically valid (as the term is used with animal studies, e.g. Koolhaas et al. Cur Dir Psychol Sci, 15(3), 2006.), and emphasizes the importance of the research question, and in the scope of this text, the "concept" that needs to be reproduced.

Response: I have reviewed the citations provided and while they discuss matters of ecological validity, I did not find a discussion of why oral morphine is a valid animal model. The Kafkafi et al. (2018) paper is about phenotyping, reproducibility, replicability and translation. The Koolhaas et al. (2006) paper is about stress models. While these might speak to the validity of animal models generally, they do not improve the validity of oral morphine in addiction studies. I have added text to this paragraph to better explain that oral morphine is unpalatable to rats and suppresses their consumption (referencing Fuentes et al., 1978). I also emphasise that in the first Rat Park paper, they provided unsweetened morphine and they had several animals die. All subsequent studies used a morphine-sucrose solution.

Fuentes, V. O., Hunt, W. B., & Crossland, J. (1978). The production of morphine tolerance and physical dependence by the oral route in the rat. *Psychopharmacology*, 59, 65-69. doi:10.1007/BF00428032

Also, the group-housing studies made prior to Alexander et al. are given rather much space in the manuscript, yet I fail to see what they bring to the main argument(s) of the text.

Response: I have amended this section to discuss the importance of this contemporaneous work to the idea of conceptual replication. I argue that how well Rat Park's results fit in with the other similar work being done at the time is suggestive of whether Rat Park is conceptually replicable. Rat Park replicated the key findings of these studies – that social and environmental factors were important – and extended them to suggest that social and environmental enrichment reduced opioid consumption.

Altogether, I believe the viewpoint and the topic themselves are important and I would love to see them as a critical review, but this text needs more revising before it can be considered as such. The current manuscript might work as a good starting point, but the main message needs to be more concisely present throughout the text, and a more critical appraisal of the criteria of reproduction and replication needs to be added, especially in the light of the target journal.

Response: I have added more explicit discussion of the criteria for direct vs conceptual replication. While I believe Nosek and Errington's (2020) recent definition of replication overlaps heavily with conceptual replication insofar as both emphasise a study's impact on theory, I have also drawn apart differences between them, such as when conceptual replication with amphetamine studies might be considered a generalisability study by Nosek and Errington.