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31st March 2023

PCI Registered Report: Stage 2 Resubmission, Round 1

Dear Recommender Chris Chambers and PCI Review Panel,

Please find submitted the revised Stage 2 manuscript (round 1) '*Does childhood adversity alter opioid drug reward? A conceptual replication in outpatients before surgery*'. We hope that we have fully addressed the comments in our point-by-point response below. We would like to thank the reviewers for their positive and helpful evaluations of the manuscript.

We look forward to the opportunity for consideration with PCI-RR.

Kind regards,

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Your decision for round #1 : *Revision needed*

Minor Revision

The three reviewers from Stage 1 returned to evaluate your Stage 2 manuscript, and I'm happy to see that their evaluations are unanimously positive. There are, however, some useful comments that should help further refine the final article, including suggestions for presentation of results, clarifying the interpretration, and new content for the Discussion. We look forward to receiving your revised submission in due course.

> *We would like to thank yourself and all reviewers for your helpful comments on the manuscript.*

by **Chris Chambers**, *07 Mar 2023 13:56*
Manuscript: **https://osf.io/jzpc2?view_only=4238d2ee3d654c4f908a94efea82a027**
version: v1 dated 02/02/2023

Review by anonymous reviewer, 01 Mar 2023 20:45

In this manuscript, the authors present the results of an observational study in which they examine the relationship with childhood adversity and ratings of subjective drug effects in response to pre-surgical administration of mu-agonist drugs. The authors hypothesized they would conceptually replicate their previous finding that childhood trauma is related to increased opioid liking. Contrary to their hypothesis, they report a significant negative association between childhood adversity and opioid liking, and no significant relationship between childhood trauma and ratings of "feeling good." Overall, this is a well-written manuscript describing an important research question and the authors have made every effort to conduct the study in accordance with their pre-registered plan.
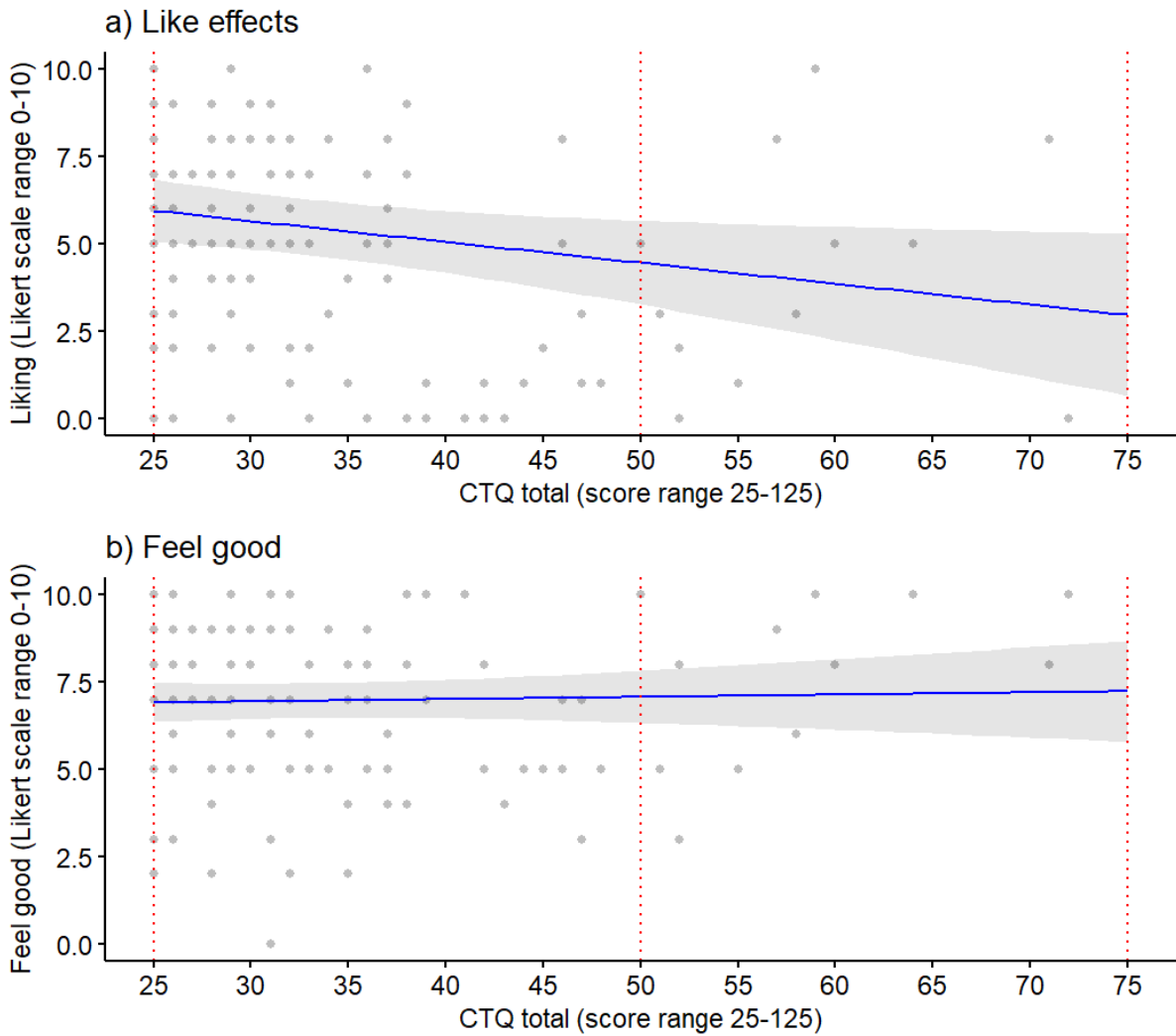
Thank you for taking the time to review both our Stage 2 manuscript, and for your helpful comments. We hope we have addressed these below.

Intro/methods: The introduction and methods do not deviate substantially from the earlier submission.

Results/discussion: Overall, the results and discussion are clearly presented.
-It would be nice to have a figure depicting the main results for H1 and H2.

> *Thank you for this comment. We have now added a plot for the results in the manuscript (Figure 2), as follows:*

a) Like effects

b) Feel good

Figure 2. Overlay of scatter plot and regression line (with the shaded 95% confidence interval band)~~Illustration of M~~*main findings from the respective models adjusted for* ~~for~~ *for the effect of childhood adversity on post-opioid a) liking of the* ~~e~~*-effects and b) feeling good. There was a modest yet significant effect of childhood adversity (CTQ total score) on post-opioid liking (b = -0.06, p = 0.046)*~~,~~ *where an average 1 Likert unit increase across all of the CTQ items (rated on a 1-5 Likert scale) led to a significant -1.5 NRS unit decrease in liking. There were* ~~and~~ *no significant effects of CTQ total score on feeling good (b = 0.01, p = 0.690)*~~.~~*. While the range of the CTQ total score is 25-125, the maximum score did not exceed 72 in this patient population. The red dotted vertical lines crossing the x-axis are to visually illustrate total scores with an average 1 Likert unit difference for the CTQ items* ~~(equivalent to a 25-point increase~~*difference* ~~in the CTQ total~~ *sum* ~~score (range 25-125)~~*), starting from the lowest total score.* ~~total~~ *The regression lines and respective models adjusted for age, sex, weight, opioid type, and surgery type. As these variables were mean-centred prior to plotting, the regression line reflect predicted liking and feel good averaged across gender, drug, age, and weight for an individual that is undergoing the most common surgery (minor abdominal surgery)*

-One interesting thing the authors note in passing, but may deserve more attention, is the fact this study was conducted on participants in a high stress environment (just before a surgical procedure). Since some work by the authors has been done addressing the context in which opioids have different effects (Loseth, Guro E., Dan-Mikael Ellingsen, and Siri Leknes. "State-dependent μ-opioid modulation of social motivation." Frontiers in behavioral neuroscience 8 (2014): 430.) it may be worth pointing out this context more explicitly in the introduction, or at least referencing this idea of state-dependent differences in opioid effects in the discussion.

> *Thank you for this very helpful suggestion! We agree that this is important, and have now indicated this more clearly and cited the Loseth et al paper in the discussion, as follows:*
>
> *Page 18: "The pre-existing stress experienced as part of surgery may limit or alter the subjective effects of opioids, in line with the 'state-dependent' perspective of opioids on behaviour (39). Different psychological responses to the acute stress of surgery in patients with greater childhood adversities could have contributed to ~~The relatively~~ lower opioid liking ~~among patients with greater childhood adversity histories could be related to psychological responses to the stressor~~ e.g., an increased desire to remain in control."*

-In discussing the failure to replicate their previous findings, it would be helpful to include a paragraph on how the demographics of the two samples compare to one another.

> *Thank you for this point. We have now included a supplemental table in SM2 with demographic differences between the two studies, and included interpretation of this within the discussion, as follows:*
>
> *Discussion Page 19: "Demographic differences between this patient sample and the prior study sample, such as older age and higher body weight (kg), may have contributed to different drug effects."*
>
> *Methods page 14: " SM2 also contains demographic variables between this and the previous sample, in addition to mean differences and confidence intervals for each of the drug effects."*

Review by Zoltan Dienes, 16 Feb 2023 20:07

The authors have carried out the analyses as planned, with additional analyses in a separate results section. The discusson draws reasonable conclusions from these results. It is clearly written. I just have a few points to make:

> *Thank you for taking the time to review both our Stage 1 and Stage 2 manuscript, and for your helpful comments throughout. We hope we have addressed your comments below.*

1) In the discussion a non-significant result is taken to support the absence of a relationship ". Exploratory subgroup analysis restricted to patients matching the groups included in the original study ('none' or 'severe' in at least one CTQ domain) showed a non-significant pattern of change in feeling good that was consistent with the original study, providing very

preliminary support for a non-linear effect of childhood adversity that should be examined with greater sample sizes. " Just a minor tweak - it is not that the non-significant result supports a non-linear relationship, as allows it as possible. So I suggest replacing "providing very preliminary support for" with "allowing for".

> *Thank you for this helpful suggestion and elaboration on this point. We have now made this change.*

2) Raw regression slopes are given, which is good, but they are hard to interpret. The authors do explain the units for one of them - but that explanation does not seem to match the description of the scales. I always do the following which makes life a lot easier: report in terms of response averaged over items. So feeling good is on a 11-pt Likert scale and each item of the CTQ is on a 5-point Likert scale (not percentage points). I would report the slope as "X Likert units of liking/Likert unit of CTQ", and label the units as such everytime a slope, SE or CI is reported. Now we know what we are talking about in terms of the units the subjects responded with. It gives a clearer sense of how big or small an effect is. (Correspondingly, I report all means and SDs in the same averaged-over-items units - I don't want to tell other researchers to do this as the original total scale may have some meaning for them; but when it is my research I always do this. And I report corresponding effects from other papers in such units as well, for comparison, even though the original authors probably reported in some meaningless total scale. I think reporting total scores hides a lot.) But I leave the exact raw units the authors wish to use up to them; just notate them each time a raw slope is given so it is clear what they are.

> *Thank you for this helpful comment. We have now added this clarification in line with your suggestion for each beta reported in the text, and also in our additional figure 2. We have tried to explain to readers what is meant by the average Likert unit increase and used this instead of the previous explanation. These changes are as follows:*
>
> *Page 12: "In the tests of the preregistered hypotheses, regression analyses indicated a modest yet significant effect of childhood adversity on post-opioid liking (b = -0.06, 95%CIs [-0.11 – -0.01], p = 0.046; Holm-Bonferroni corrected, Table 2), indicating a negative association between total CTQ score and liking (Figure 2). — when adjusting for opioid type, age, sex, weight, and operation category. As the CTQ total score is the sum of 25 items answered on a 1 to 5-point Likert scale (range 25-125), an average 1 Likert unit increase across all items would equate to a 25-point increase in the CTQ total score. Thus, for each average 1 Likert unit increase on the CTQ, we would expect a decrease in 1.5 numeric rating scale (NRS) units of liking. score 25 increase in the. 25 units higher, where pPredictions drawn from the model would be that there is a 0.6-point decrease in Liking with each 10-point increase in severity score on the CTQ (i.e., 10% of the total score's possible range) would lead to a 0.6-point decrease for liking, there is a corresponding 1.5 unit l,when after adjusting for opioid type, age, sex, weight, and operation category and pre-drug score. The regression analyses also identified showed a significant effect of surgery type, with patients undergoing minor gynaecological surgery reporting significantly less liking than patients undergoing minor abdominal surgeries (b = -2.28, 95%CIs [-3.91 – -0.64], p = .014).*
>
> *For post-opioid feeling good, there was no significant effect of CTQ score (0.25 NRS units of change in feel good, per average increase in 1 Likert unit of the CTQ; b =*

0.01, 95%CIs [- 0.03 – 0.04], p = 0.690; Holm-Bonferroni corrected, Table 2). The only significant predictor for post-opioid feeling good was pre-opioid feeling good (0.71 NRS units of change in post-opioid feel good, per average increase in 1 NRS unit of pre-opioid feel good; b = 0.71, 95%CIs [0.55 – 0.87], p <.001). Residuals for feeling good regression deviated from normality, however bootstrapped estimates did not differ significantly from the original model. No other predictors were significantly associated with the two outcomes. Both model regression outcomes are presented in Figure 2."

Figure caption (page 14): "Figure 2. Overlay of scatter plot and regression line (with the shaded 95% confidence interval band) Illustration of M main findings from the respective models adjusted for for for the effect of childhood adversity on post-opioid a) liking of the e effects and b) feeling good. There was a modest yet significant effect of childhood adversity (CTQ total score) on post-opioid liking (b = -0.06, p = 0.046), where an average 1 Likert unit increase across all of the CTQ items (rated on a 1-5 Likert scale) led to a significant -1.5 NRS unit decrease in liking. There were and no significant effects of CTQ total score on feeling good (b = 0.01, p = 0.690). . While the range of the CTQ total score is 25-125, the maximum score did not exceed 72 in this patient population. The red dotted vertical lines crossing the x-axis are to visually illustrate total scores with an average 1 Likert unit difference for the CTQ items (equivalent to a 25-point increase difference in the CTQ total sum score (range 25-125), starting from the lowest total score. total The regression lines and respective models adjusted for age, sex, weight, opioid type, and surgery type. As these variables were mean-centred prior to plotting, the regression line reflect predicted liking and feel good averaged across gender, drug, age, and weight for an individual that is undergoing the most common surgery (minor abdominal surgery)"

3) Optional. In raw units, can the authors report a confidence interval on the difference in feeling good and liking between the two extreme groups, identified as in the original study, and compare what the difference was for the original study (e.g. about 18 points on a 0-100 euphoria scale? So about 2 units on a 0-10 feeling good scale). If the CI includes the original study's value then there is not a failure to replicate by an analysis close to the original study's. Just a quick rule of thumb for making sense of the results.

This is a great suggestion! We have now added an additional table to the supplementary material containing the MD and Cis between the severe and none groups for this and the previous study.

Results page 14: "Additional data and figures comparing these groups are available in SM2, including scatterplots where visual inspection did not indicate a clear linear or nonlinear pattern. SM2 also contains demographic variables between this and the previous sample, in addition to mean differences and confidence intervals for each of the drug effects."

Discussion page 19: "Mean differences and confidence intervals for post-opioid liking and feeling good were not comparable to the previous study."

Review by Yuki Yamada, 03 Feb 2023 04:58

This is a Stage 2 manuscript in which I previously reviewed a Stage 1 manuscript and analyses were performed according to the protocol that IPA was granted. As I mentioned in Stage 1, I am not an expert on this topic, so I cannot make good points on the theoretical aspects. However, I can at least admit that the main hypothesis was not supported by this analysis, or rather that a weak opposite effect was observed. I agree with the authors about the possibility that the sample size issue in this case, including the exploratory analysis, may not have ensured its coverage or verified its linearity. On the other hand, it is worthwhile to publish this study because the exploratory investigation has identified some promising possibilities for future research. Minor points are noted below. Overall, no major problems were found.

> *Thank you for taking the time to review both our Stage 1 and Stage 2 manuscript, and for your helpful comments throughout. We hope we have addressed these below.*

- Some minor changes to the introduction and methods are observed, but most of them are probably only modifications to the citation numbers, so there is probably no problem.

> *Thank you for spotting this. There should be no changes in the introduction. In the methods we made some very minor changes such as the inclusion of a citation, and addition of the word in page 6 of the methods (page 6) 'In the rare case of repeated responses', and (page 8) 'Data ~~was~~were analysed' and other minor typological errors. We hope these minor changes are not a problem for the registered report process and can revert them if necessary.*

- There are analyses that are not included in the Stage 1 manuscript as "Exploratory analyses", but it would be good to state clearly that these are not registered so that readers who do not rigorously check the Stage 1 manuscript will not be misled.

> *Thank you for this point. To increase clarity for readers we have adjusted the subtitles for each exploratory section to include 'exploratory', as follows:*

> **3.3 Exploratory ~~analyses 3.3.1 S~~subgroup analyses comparing high childhood adversity with none for 'feeling good' and 'feeling anxious'**

> **3.~~3.2 4~~ Exploratory ~~Childhood adversity~~ regressions for ~~and~~ other subjective drug effects**

> **3.~~3.3~~5 Exploratory ~~Associations~~ correlations with mental health, alcohol and other drug use, and related constructs**

> *We have also added extra details to increase clarity for this in section 3.3 and section 3.5, as follows*

> *Page 14 "While the positive mean change in feeling good scores for the severe group is consistent with the original study results, post-hoc exploratory ~~an~~ ANOVA's ~~exploring~~ comparing the interaction between group ('none', 'severe') and time (pre, post) did not yield a significant interaction effect for feeling good (F(1,89) = 3.45, p = .067), nor any significant main effects. The ANOVA of anxiety ratings did not show*

any significant interaction effects (F(1,87) = 1.69, p = .202).These were exploratory analyses that were not included in the registered report."

Page 16 "displays the exploratory correlations…"

Section 3.3 already specifies the regressions as exploratory in text e.g., ", exploratory regression models indicated…"

Necessary changes required for submission to fulfil requirements for PCI-RR:

1. *We have updated the declarations of interest statement in line with the PCI-RR requirements:*

Page 21: "The authors of this article declare that they have no financial conflict of interest with the content of this article. None to declare."

2. *We have elaborated on the data sharing statement for why the data is not open access:*

Page 8: "The data has not been made publicly available due to the sensitive nature regarding health and adversity. The conditions of our ethical approval, and the constraints of Norwegian law, prevent sharing of the data supporting this research with any individual outside the author team under any circumstances."