Reply to Beckers, McIntosh and Chambers on the verification of 'preventing the return of fear using retrieval-extinction in humans'

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A recent article in the journal Cortex (Chalkia et al. 2020a) has claimed a failure to verify the results reported in our 2010 study describing the phenomenon of reconsolidation updating using the retrieval-extinction protocol (Schiller et al., 2010). Since the journal did not grant us the right of reply, we publish our response here. We show, among other things, that ***a reanalysis of the raw data reproduces the results and contend that the conclusions are valid.***

What is a verification report?

The purpose of this new type of report is supposedly to reanalyze the original data in an effort to reproduce the results. However, in this case the verification report also contained new analyses and critiques. The authors not only acted as auditors of the data but also as reviewers for a study that has already been reviewed and replicated multiple times. The verification report was in fact able to reproduce the results almost entirely, with minor exceptions that do not alter the conclusions of the original report (see below). Therefore, ***the verification report achieved its purpose – it showed that the original study was valid, which should have been the conclusion of the report.*** Yet, the report further included additional analyses and arguments against the original approach. There is room for such scientific discourse, but these efforts do not invalidate the original study. By claiming that they do, the verification paper is being presented as the ultimate arbitrator for standards in the field. However, it should be presented for what it is – an opinion piece on a decade old study.

Below, we provide point-by-point response to the major claims raised in the verification report and in the accompanying editorials. We also discuss the consequences of the editorial process on norms for open science. We conclude that the retrieval-extinction effect is a viable phenomenon that has been extensively vetted by the scientific community.

<u>Claim</u>: Replication attempts of the original study are few and have yielded mixed results.

To date, there have been at least 51 published replication studies of retrieval-extinction in humans and in clinical populations, with over 70% success (Table 1)**.** Only a few of these replications were mentioned in the verification report. In addition, many more replications have been demonstrated in rodents (for review, see Lee et al., 2017,) some including detailed cellular and molecular analyses differentiating the neural signatures of extinction and retrieval-extinction (e.g. Monfils et al., 2009; Cahill & Milton 2019). Given multiple replications and translation implications for clinical populations, ***which attest to the veracity and reproducibility of the***

***original study**,* the assertions that issues with the original study have hampered progress in the field are unjustified.

<u>Claim</u>: The verification report was unable to verify the results reported in the original study.

The verification report was in fact able to reproduce the results almost entirely. The claims made in the verification report are not about the data per se; rather, these are assertions regarding the screening procedure and choice of analyses. The opinions expressed in the verification report are valuable, but no more than those of the editors and reviewers of the original study and the multiple authors that have replicated the effect since. It is misleading to present opinions regarding alternative methodological approaches as a verification failure; these views should be expressed in a separate opinion paper to avoid conflation with verification success.

<u>Claim</u>: Exclusions made post-hoc influenced the results.

Most participants that did not show measurable responses or evidence for learning did not continue to the next day – a process that eliminates post-hoc exclusions. Of excluded participants, the vast majority (over 70% for study 1 and 90% for study 2) were discontinued *prior* to day 3 because they did not learn, leaving little data to assess post-hoc. In the few cases in which data could not be fully analyzed before Day 3, full data sets were collected before determining exclusions. The original article only reported exclusions from participants with complete datasets and misstated the exclusion criteria, which led us to publish an addendum to the original study (Schiller et al., 2018). Importantly, the failure to initially report exclusions of participants who were discontinued before study completion has no bearing on the issue of post-hoc exclusions.

<u>Claim</u>: Experimenter decisions regarding exclusion cut-off influenced the retrieval-extinction effect.

The retrieval-extinction effect remained intact under all exclusion cut-offs assessed in the verification report. The verification report only found that the *control groups* failed to show spontaneous recovery in alternative samples. This is a trivial exercise: including participants that did not learn on Day 1 is bound to reduce retrieval levels on Day 3 since there is no memory to retrieve. Evidence for any influence of the exclusion cut-off on the retrieval-extinction effect would have been indicated by memory *emerging* in the experimental group, but this was not the case for any alternative sample. In fact, differences between the experimental group and the control groups were still observed under the most lenient threshold regardless of how the final sample was selected.

<u>Claim</u>: Successful replication of the retrieval-extinction effect depends on high exclusion rates.

Studies that have successfully replicated the retrieval-extinction effect have participant exclusion rates ranging from 0% to over 50%, demonstrating this effect is not dependent on exclusion criteria or rates.

<u>Claim</u>: Statistical tests of the recovery effect were inappropriate.

An opinion about an alternative analysis is not the same as an error with the original analysis. The primary hypothesis of the original study was that there should be differential responding between the groups on Day 3, which was confirmed with an ANOVA. Independent t-tests were used to demonstrate this was due to lack of recovery in the reminder group. The reviewers and editors of the original study, and authors of many subsequent replications, found this analysis appropriate and convincing. The verification report presented the *opinion* that an interaction in an ANOVA including Day 2 and Day 3 is more appropriate. This reanalysis yielded a trend of an interaction, which along with the clear, directional *a priori* hypothesis, would merit the follow-up *t*-tests showing the primary hypothesized effect, once again verifying the findings of the original report.

<u>Claim</u>: Failure to reproduce critical evidence for reinstatement in study 2.

The analysis reported in the verification report fully supports reinstatement in study 2. The specific trials analyzed in the verification report ANOVA were not the same as those indicated in the original paper, but we agree that the alternative analysis used in the verification paper is an appropriate one. This analysis reproduced all the effects reported in study 2 with the exception of one interaction in the re-extinction phase (stimulus x time). However, this analysis also yields a main effect of stimulus and a significant difference between the stimuli in re-extinction, which *is* the critical test for reinstatement (see OSF repository). Furthermore, the verification report successfully replicated the follow-up analyses demonstrating that reinstatement was only observed for the non-reminded conditioned stimulus. The stimulus x time interaction only adds that the difference between the stimuli decreased over time during re-extinction, which is *not* the critical test of reinstatement. The reanalysis therefore verified all effects and supports all conclusions.

Altogether, the major claims raised in the verification report were unsubstantiated. ***All effects can be reproduced from a reanalysis of the raw data and the conclusions remain valid***. The calls made in the verification report and in the accompanying editorials to disregard the original study are out of line. Although presented as such, these calls are *not* based on the data per se but rather reflect subjective views.

A comment on the editorial process

There are a few disturbing issues here: **1)** publishing a verification report without the original authors' response does not allow the scientific community to weigh the evidence and see the whole picture; **2)** the publication process for this verification report involved collaboration between the authors and the editors throughout, which has the potential to influence editorial objectivity; **3)** while data debates are welcomed, the editors crossed the line to derogatory editorials that failed to acknowledge the extensive vetting of our finding, and launched a social media campaign lauding the efforts of the editors and authors that are irrelevant to scientific discourse.

By having an opaque publication process, along with a social media campaign, while failing to provide the authors of the original study the opportunity for a concurrent public response, ***the editorial team maintains full control of the narrative, and the unchecked power to attack any random paper or scientist***. This is a dangerous weapon in the name of transparency and open science.

Moving forward

Research on reconsolidation has exploded in the last two decades, with hundreds of studies delineating the neurobiology of reconsolidation mechanisms. Beyond pharmacological blockade, reconsolidation updating via behavioral means has been especially valuable for humans due to its non-invasive nature. The phenomenon of retrieval-extinction is situated within that realm, as one of multiple behavioral methods for memory modification, among various protocols and memory systems.

Following the initial reports of the retrieval-extinction effect in rats (Monfils et al., 2009) and humans (Schiller et al., 2010), subsequent research has further demonstrated retrieval-extinction interference in mice, rats and humans (for reviews see, Auber et al., 2013; Agren, 2014; Lee et al., 2017; Monfils and Holmes, 2018; Cahill and Milton, 2019; Phelps and Hofmann, 2019; see also Table 1). Additional demonstrations of retrieval-extinction were shown in juvenile rats (Jones and Monfils, 2016) and adolescent humans (Johnson and Casey, 2015). Variations on the effect include retrieval followed by vicarious extinction (Golkar et al., 2017) and imaginal extinction (Agren et al., 2017). Epigenetic priming was shown to enable retrieval-extinction interference of remote memories (Graff et al., 2014); and studies have demonstrated engram-specific manipulation of retrieval-extinction (Khalaf et al., 2018). Reconsolidation updating using other forms of behavioral and non-invasive interference has also been reported (Lee, 2009; Lee et al., 2017; Borgomaneri et al., 2020).

The retrieval-extinction procedure has further been shown to be effective in clinical populations, including heroin addicts (Xue et al., 2012), tobacco smokers (Germeroth et al., 2017), and PTSD (Vermes et al., 2020) and phobia patients (Bjorkstrand et al., 2016; Maples-Keller et al 2017), with long-lasting effects (Bjorkstrand et al., 2017). Some forms of therapy, such as coherence therapy, are built on the principles of memory reconsolidation updating and are designed to maximally optimize this process (Lane et al., 2015; Gray et al., 2019; Vaz and Ecker, 2020).

About 28 percent of replication attempts in humans fail to demonstrate the retrieval-extinction effect (Table 1). Theoretical formulations (Gershman et al., 2017) and empirical work suggest that inconsistencies in reconsolidation effects may depend on the degree of memory destabilization, as not every memory recall involves neural destabilization; or on the efficacy of the interference, which could differ across individuals and populations (e.g., Cassini et al., 2017; Hu et al., 2018; Cahill et al., 2019; Junijao et al., 2019; Yang et al., 2019; Kitamura et al., 2020).

Of this vast literature, the verification report mentioned only a few studies; and the authors' failed replication of retrieval-extinction (Chalkia et al., 2020b) selectively cited 7 successful and 7 failed replications only. Such imbalanced representation of the literature creates a false picture of the actual state of the science of the retrieval-extinction effect in humans. The senior author of the verification report has also published failed replications of similar phenomena in rodents including retrieval-extinction and reconsolidation blockade of context and cued fear memories (Luyten and Beckers, 2017; Alfei et al., 2020; Luyten et al., 2020). All of these studies make overarching claims casting doubt about the reconsolidation phenomenon itself. However, the validity of reconsolidation does not rely on one study or one laboratory, but rather is reflected in the aggregate evidence across species, methods, laboratories and memory domains. A more nuanced, informed, and scholarly discussion is required to fit the pieces of evidence together into a coherent and complete understanding of the reconsolidation phenomenon, its limits, and the claims of the verification report and the accompanying editorials.

A major hurdle for studying reconsolidation updating in humans is the lack of an objective measure for memory destabilization. Studies have attempted to identify parameters that will reliably induce destabilization, such as the use of reminders that elicit prediction error (e.g., Krawczyk et al., 2017). But without direct indices of memory destabilization, memory updating is presumed from behavioral modification, and replication failures could be due to a number of factors, including failed destabilization, failed interference, or another process altogether. This leaves us with an infinite parameter space, which renders replication failures difficult to conclusively interpret. The same issue applies to behavioral reconsolidation interference and the pharmacological disruption of reconsolidation in humans, which could be effective only under a specific set of conditions.

Fortunately, studies with animal models verify memory destabilization following reactivation, including with the retrieval-extinction paradigm, but this research also shows that destabilization following reactivation depends on criteria that are not yet fully specified (Cassini et al., 2017; Cahill et al., 2019; Cahill and Milton, 2019). A viable path forward for human studies would be to examine a wide parameter space in order to build mechanistic and computational insights in hopes of converging on a highly dependable procedure designed by those insights (e.g., Hu et al., 2018; Junijao et al., 2019; Yang et al., 2019; Kitamura et al., 2020). Another, more challenging path is the attempt to discover a human biological marker, such as a measurable neural state of destabilization/reconsolidation. Some studies have already begun identifying computational and neural indices of reconsolidation updating in the human brain (e.g., Agren et al., 2012; Schiller et al., 2013; Feng et al., 2016; Gershman et al., 2017; Junijao et al., 2019).

In summary, the phenomenon of reconsolidation is backed by an extensive body of evidence comprised of hundreds of studies covering multiple levels of investigation across species and domains of memory. While reconsolidation updating is not yet fully understood, and its conceptualization may evolve with new approaches and techniques, it is a well validated finding supported by both neurobiological and behavioral evidence. Contrary to claims of the verification report and accompanying editorials, our study represents an important contribution to this growing literature.

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OSF repository – https://osf.io/jhu5c/

Table 1. Successful and failed replications of the retrieval-extinction effect in humans. The list is not intended to be exhaustive and is based on search through PubMed and studies citing the original study.

Successful replications (37 experiments)	
Study	**Comments**
Agren et al 2012 Science 337: 1550-1552	100% reinforcement rate; 2min reminder
Agren et al 2012 Transl Psychiatry 2: e76	100% reinforcement rate; 2min reminder; the effect was influenced by dopamine and serotonin- related genes
Oyarzun et al 2012 Plos One 7: e38849	Aversive auditory US
Schiller et al 2013 PNAS 110: 20040-20045	Replication of reminder specificity
Liu et al 2014 Biol Psychi 76: 895-901	9 experiments with either US or CS reminders
Steinfurth et al 2014 Learn Mem 21: 338-341	The effect seen with either a one-day old or a week-old memory
Bjorkstrand et al 2015 Plos One 10: e0129393	An 18-months follow up
Johnson & Casey 2015 Sci Rep 5: 8863	Similar effects in adults and adolescents
Asthana et al 2016 Int J Neuropsychopharmacol 19: 1-9	The effect moderated by *BDNF* polymorphism
Feng et al 2016 Soc Cogn Affect Neurosci 11: 991-1001	Fear pictures as US
Thompson & Lipp 2017 Behav Res Ther 92: 1-10	US reactivation with fear relevant and fear irrelevant stimuli
Agren et al 2017 Behav Brain Res 319: 9-15	100% reinforcement rate; 2min reminder; standard and imaginal extinction
Golkar et al 2017 Behav Res Ther 92:87-93	High reinforcement rate; fear relevant stimuli; vicarious extinction
Hu et al 2018 Sci Rep 8: 8848	The effect seen with short but not long reminder durations
Junjiao et al 2019 Cortex 121: 292-307	Destabilization depends on prediction error
Yang et al 2019 Behav Res Ther 122: 103461	Destabilization influenced by uncertainty
Kitamura et al 2020 Neurobiol Learn Mem 174: 107285	The effect seen with both high and low reinforcement rates
Successful replications in clinical populations	
Xue et al 2012 Science 336: 241-245	Reduced craving in heroin addicts
Bjorkstrand et al 2016 Curr Biol 26: 2690-2695	Enhanced approach behavior in Spider Phobia
Bjorkstrand et al 2017 Behav Brain Res 324: 125-129	Spider Phobia – 6 months follow up
Germeroth et al 2017 JAMA Psychiatry 74: 214-223	Reduced craving and cigarette consumption in smokers
Maples-Keller et al 2017 Depression & Anxiety	Reduced physiological responses using virtual reality exposure therapy in phobia

Vermes et al 2020 J Affect Dis 276: 487-494	Reduced physiological responses using imaginal exposure in PTSD
Replication failures (14 experiments)	
Soeter & Kindt 2011 Learn Mem 18: 357-366	High reinforcement rate; fear-relevant stimuli
Golkar et al 2012 Front Behav Neurosci 6: 80	Fear-relevant and fear-irrelevant stimuli
Kindt & Soeter 2013 Biol Psychol 92: 43-50	High reinforcement rate; fear-relevant stimuli; expectancy ratings
Warren et al 2014 Neurobiol Learn Mem 113: 165-173	100% reinforcement rate; with and without expectancy ratings
Meir Drexler et al 2014 Behav Neurosci 128: 474-481	High reinforcement rate; fear-relevant stimuli; expectancy ratings
Klucken et al 2016 Cortex 79:112-122	No COMT Val^{158}Met-polymorphism effect
Fricchione et al 2016 Psychophysiology 53: 1343-1351	High reinforcement rate; fear-relevant stimuli
Kredlow et al 2018 Behav Res Ther 108: 45-57	Healthy and anxious individuals; strong acquisition; but weak reinstatement effect in controls
Zimmermann & Bach 2020 Learn Mem, 27: 164-172	Weak reinstatement effect in controls
Chalkia et al 2020 Cortex 129: 496-509	Direct replication

* US, unconditioned stimulus; CS, conditioned stimulus