Biological Psychiatry: Celebrating 50 Years

Techniques and Methods

Fear Extinction Retention: Is It What We Think It Is?

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There has been an explosion of research on fear extinction in humans in the past 2 decades. This has not only generated major insights, but also brought a new goal into focus: how to maintain extinction memory over time (i.e., extinction retention). We argue that there are still important conceptual and procedural challenges in human fear extinction research that hamper advancement in the field. We use extinction retention and the extinction retention index to exemplarily illustrate these challenges. Our systematic literature search identified 16 different operationalizations of the extinction retention index. Correlation coefficients among these different operationalizations as well as among measures of fear/anxiety show a wide range of variability in four independent datasets, with similar findings across datasets. Our results suggest that there is an urgent need for standardization in the field. We discuss the conceptual and empirical implications of these results and provide specific recommendations for future work.

Keywords: Extinction recall index, Extinction retention index, Fear conditioning, Meta-research, Retrieval index, Systematic literature search

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In 2006, Anderson and Insel (1) stated that "The development of new approaches to anxiety disorders based on the neurobiology of fear extinction represents perhaps the best current opportunity for translating neuroscience discoveries into clinical applications[…]." Since then, there has been an enormous growth in fear extinction research [e.g., (2–6)], which continues 2 decades later (7,8). This has not only generated major insights into extinction mechanisms (7,9–12), but also brought a new goal into focus: "The current challenge however is not how to *achieve* fear reduction [i.e., extinction], but rather to *maintain* it over time [i.e., extinction retention]" (8). Here, we argue that despite decades of research, there are conceptual and procedural challenges that urgently need to be addressed for experimental research on extinction retention to successfully translate into clinical applications.

Extinction and Extinction Retention: Conceptual Challenges

Extinction has been typically investigated in fear conditioning experiments[1] (13): Acquisition of conditioned fear is achieved by presenting an initially neutral stimulus (conditional stimulus [CS+]) paired with an aversive event (unconditional stimulus [US]), which generates a fear (CS+/US) memory (a procedure termed fear acquisition training). While rodent work typically includes only a CS+ (single-cue protocols), human work typically includes a second stimulus (nonconditioned stimulus [CS−]) not followed by the US (differential protocols). Importantly, conditioned responding is quantified as differential responding [(CS+) − (CS−)] in differential protocols.

When the CS+ is no longer followed by the US for a sufficient number of trials, the conditioned response gradually disappears (a procedure called extinction training). The contemporary view is that the original conditioned fear memory is not erased, but rather inhibited by a competing extinction memory (14). Upon presentation of the CS at a later time (i.e., retention test), the dominance of one of these memories over the other determines whether fear is expressed (fear retention) or not (extinction retention). Experimental protocols designed to investigate extinction retention [e.g., (15)] sometimes include two different CS+ types during fear acquisition, with only one being subsequently extinguished (extinguished CS+ [CS+e]), while the second is not presented during extinction training (unextinguished CS+ [CS+u]). Methods in human fear conditioning are heterogeneous, and even subtle procedural variations affect learning processes [discussed in Lonsdorf *et al.* (13)]. The term "extinction retention" has been used to refer to different procedural scenarios (13). Typically, a test phase following (e.g., 24 hours after) extinction training is referred to as the extinction retention phase. However, strictly speaking, this is appropriate only when contextual manipulations that likely trigger dominance of extinction over fear memory are employed—such as the test phase taking place in the

[1] We acknowledge recent discussions suggesting the term "threat conditioning" (46). The majority of studies included here used "fear conditioning." Hence, using a different term may lead to confusion.

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extinction learning context (i.e., $A_{acq}B_{ext}B_{test}$). In the absence of such manipulations (i.e., $A_{acq}A_{ext}A_{test}$ paradigm), there is no reason to believe that the extinction memory is more likely to be retrieved than the fear memory. This is illustrated by "spontaneous recovery," a term often used to refer to the same procedure as extinction retention (13). Here, as noted previously (5,13), the distinction between procedure and process is of utmost importance. More precisely, we argue that a test phase (i.e., procedure) following extinction should atheoretically be referred to as a retention test (13), during which the reoccurrence of conditioned responding or its absence may be observed or hypothesized. Accordingly, the two processes underlying the observed results should be referred to as "return of fear" and "extinction retention," respectively.

Extinction and Extinction Retention: Procedural Challenges

The operationalization of extinction and extinction retention also varies widely [see Lonsdorf *et al.* (13)], which we illustrate here by using the extinction retention index (ERI) as an example.

The ERI—as employed in rodent work using freezing [e.g., (16)]—was introduced to the human field using skin conductance responses (SCRs) (17–19) as a cross-species translational tool. The ERI followed on the idea that the strength of the response during a retention test can be expressed as the percentage of the strength of such response during fear acquisition (i.e., "How much of the acquired fear comes back?"). For illustration, consider two individuals, one ("X") showing higher maximal SCR CS+ responses (1 μS) than the other ("Y") during acquisition training (0.5 μS). Subsequently, both individuals undergo extinction training. During a later retention test, both individuals display the same amount of CS+ responses (i.e., 0.5 μS). Consequently, individual X's extinction retention would be considered more efficient than individual Y's, as he/she shows fewer CS+ responses at the retention test with respect to the CS+ responses during acquisition training (based on an example provided by M.R. Milad, Ph.D., personal communication, October 23, 2018).

Since its introduction in humans, the ERI has been widely employed—in particular for SCRs—and is assumed to represent a standardized index that supports both comparability and replicability of findings. However, our systematic literature search identified 16 different calculations of the ERI using SCRs. To illustrate the potential impact of this subtle—but often unrecognized—heterogeneity, we have reanalyzed four datasets to calculate the magnitude of the correlations among these different ERIs. Our results challenge the conceptual and empirical rationale for the ERI. Finally, we provide recommendations for future work.

METHODS AND MATERIALS

We conducted a systematic literature search to identify peer-reviewed studies published until October 2018 in which an ERI was calculated using SCRs in humans (see the Supplement for details). Subsequently, we used SCR data from a published study (dataset 1, $N = 50$) (20) to recalculate the ERIs using the formulas identified by the literature search. In short, 50 healthy participants with moderate to strong fear of spiders underwent a 2-day differential (CS+, CS−) paradigm (day 1: fear acquisition and immediate extinction training; day 2: extinction retention) (see the Supplement for details). Finally, we calculated Spearman's rank coefficients among the different ERIs (see Table 1) because we were interested if the specific rank between participants changes across ERI versions. The ERIs were also recalculated in three additional datasets (datasets 2–4) all using a 2-day [i.e., immediate extinction training (21)] or 3-day [i.e., delayed extinction training (21,22)] paradigm including two CS+ conditions (CS+e, CS+u) and one CS− condition in healthy participants (see the Supplement for methodological details and results). In addition, inspired by a reviewer's comments, correlations between measures of fear/anxiety and the ERIs were calculated. In dataset 1, the Fear of Spiders Questionnaire (FSQ) (23) was used, while the State-Trait Anxiety Inventory (24) was used in datasets 2 to 4. The p values were corrected for multiple comparisons using the Benjamini-Hochberg procedure (25) separately for cross-ERI correlations and correlations between the ERIs and the FSQ and State-Trait Anxiety Inventory, respectively.

RESULTS

Heterogeneity in ERI Calculation

We identified 16 different calculations of the ERI included in 37 separate studies (see Table 1; note that three studies included two different ERI versions [ERI 2 and ERI 6 (26); ERI 9a and 9b (27); ERI 15 and 16 (28)][2]), and in total 34% of studies using SCRs during a retention test employed an ERI. In 26 studies, the retention test took place in the extinction learning context (i.e., testing for extinction retention), while in 11 studies, no contextual manipulation was applied.

The ERI calculations identified differed in a multitude of ways. First, responding during the retention test was operationalized as differential responding (i.e., difference between the CS+ and the CS−) in nine studies (henceforth referred to as differential ERIs) and as responding to the CS+ only in 28 studies [henceforth referred to as nondifferential ERIs; one study (27) used in addition a CS− based index]. Second, the number of trials the ERI was based on ranged from one to five (one: $n = 4$; two: $n = 19$; three: $n = 1$; four: $n = 13$; five: $n = 2$)—a wide range in light of rapidly occurring re-extinction due to nonreinforced CS presentations during the retention test. Third, responding during the retention test was corrected for responding during acquisition ($n = 31$ studies) or extinction ($n = 2$ studies), while also no correction was employed ($n = 4$).

Fourth, of those 31 studies correcting responding for the strength of fear learning [cf. (29)], responding during acquisition training was operationalized as the maximum response to the CS+ ($n = 9$), the CS+e ($n = 13$), any CS+ (i.e., CS+e or CS+u; $n = 1$), or any CS ($n = 1$); the average of the two largest responses to the CS+ ($n = 3$); or the differential response (maximum CS+/CS− difference; $n = 4$). The maximum CS+ response during acquisition training, however, may not be a good indicator of the strength of fear learning. For instance, in our data, the maximum SCR to a CS+ is most often observed to the first CS+ (see Figure 1A, B), which precedes the first US presentation and hence reflects arousal or orienting (30) rather than associative learning strength. In contrast, the maximum

[2] We only discuss CS+ based indices [excluding CS− based ERI 9b in Raio *et al.* (27)].

Table 1. Operationalizations and Calculations of the ERI Based on Skin Conductance Responding in the Literature as Derived From a Systematic Literature Search (Until October 2018)

Index No.	Term Used by Authors	Formula for Calculation	Specifications Used in Calculation of the ERI							Studies in Which It Was Used
			Trials Used to Assess Retention	Trial Type (Retention)	Acquisition Correction	Extinction Correction	×100	Division From 100 or 1	Recall in Extinction Context	
Nondifferential Indices (CS+ Based)										
1	% conditional response recovered (17) ERI (18,19)	100 − [100 × first CS+ of retention/max(CS+ acquisition)]	First	CS+	max(CS+)	No	Yes	Yes	Yes	(17)[a] (18,19)
2	ERI	100 − [100 × mean(first 2 CS+ retention)/max(CS+ acquisition)] OR in other experimental designs 100 − [100 × mean(first 2 CS+e retention)/max(CS+e acquisition)]	First 2	CS+[a] or CS+e[a]	max(CS+)[a] or max(CS+e[a]	No	Yes	Yes	Yes, except for (29)	(47,48) (49–51)[a] (26,52–54) (15,55)[a]
3	ERI	100 × [1 − [mean(first 2 CS+ retention)/(mean(two largest CS+ acquisition)]	First 2	CS+	2 max(CS+)	No	Yes[b]	Yes[b]	No	(56)
4	ERI	100 − [100 × mean(first 2 CS+e retention)/max(acquisition)][c]	First 2	CS+e	max(acq)	No	Yes	Yes	Yes	(57)
5	Extinction recall index/ recovery index	100 × mean(first 2 CS+ retention)/ max(CS+ acquisition)	First 2	CS+	max(CS+)	No	Yes	No	No	(58,59)
6	ERI	100 − [100 × mean(first 4 CS+e retention)/max(CS+e acquisition)][a,d,e]	First 4	CS+e[a,d]	max(CS+e)[a,d]	No	Yes[e]	Yes[e]	Yes	(26,60,61)[d] (62)[a] (26,63) (64)[e]
7	ERI	100 − [100 × mean(first 4 CS+e retention)/max(to a CS+ trial in acquisition)]	First 4	CS+e	max(CS+e and CS+u)	No	Yes	Yes	Yes	(65)
8	% fear recovery	100 × mean(first 4 CS+ retention)/ max(CS+ acquisition)[f]	First 4	CS+	max(CS+)	No	Yes	No	No (66) Yes (67)	(66,67)[f]
9a	Retrieval index	(first CS+ retention) − (last CS+ extinction)[g]	First	CS+	No	Last CS+[g]	No	No	No	(27)
Nondifferential Indices (CS− Based)										
9b		(first CS− retention) − (last CS− extinction)[g]	First	CS−	No	Last CS−[g]	No	No	No	(27)
Differential Indices										
10	ERI	100 − (100 × [(mean first 2 CS+ retention) − (mean first two CS− retention)]/max pair[h](CS+) − (CS−) acquisition)	First 2	(CS+) − (CS−)	max [pair[h](CS+) − (CS−)]	No	Yes	Yes	Yes	(68,69)
11	Extinction recall index	Mean(first 2 CS+ retention) − mean(first 2 CS− trials retention)	First 2	(CS+) − (CS−)	No	No	No	No	Yes	(20,39)
12	% suppression (extinction) rate	100 × [(mean CS− retention) − (mean CS+ retention)]/(mean CS− retention)	All (i.e., 3)	(CS+) − (CS−)	No	No	Yes	No	No	(70)
13	ERI/recovery index	100 − [100 × mean(first 4 CS+ retention) − (mean[first 4 CS− retention])/(max pair[h](CS+) − (CS−) acquisition)]	First 4	(CS+) − (CS−)	max [pair[h](CS+) − (CS−)]	No	Yes	Yes	No	(71,72)

Table 1. Continued

Index No.	Term Used by Authors	Formula for Calculation	Specifications Used in Calculation of the ERI: Trials Used to Assess Retention	Trial Type (Retention)	Acquisition Correction	Extinction Correction	×100	Division From 100 or 1	Recall in Extinction Context	Studies in Which It Was Used
14	Extinction recall index	[Mean(first 4 CS+u retention) − (mean(first 4 CS+e retention)]	First 4	(CS+e) − (CS+u)	No	No	No	No	No[i]	(73)
15	Extinction retention score	[Mean(first 5 CS+ retention) − mean(first 5 CS− retention)] − [mean(trial 2–5 CS+ extinction) − mean(trial 2–5 CS− extinction)]	First 5	(CS+) − (CS−)	No	CS+(early extinction) − CS−(early extinction)	No	No	No	(28)
16	Extinction retention score	[Mean(first 5 CS+ retention) − mean(first 5 CS−retention)] − [mean(last 5 CS+ extinction) − mean(last 5 CS− extinction)]	First 5	(CS+) − (CS−)	No	CS+(end extinction) − CS−(end extinction)	No	No	No	(28)

Note that some experimental protocols employed two different CS+ types during fear acquisition training, one of which was shown during extinction training (CS+e) and one that was not (CS+u; sometimes also referred to as CS+ne). Importantly, during the retention test, both CS+ (Cs+e and CS+u) as well as the CS− are typically presented. Similarly, in studies employing a CS+ and a CS−, both stimuli are presented again during the retention test. Differential index was based on CS+/CS− discrimination, nondifferential index was based on one CS type only.

CS+, conditional stimulus paired with the unconditional stimulus (US) during fear acquisition training; CS−, nonconditioned stimulus not paired with the US; CS+e: extinguished conditional stimulus; CS+ne, conditional stimulus not extinguished; CS+u, unextinguished conditional stimulus; ERI, extinction retention index.

[a]The original publications referred to "recall trial" and "maximum during acquisition" or "a CS+ trial." In these studies, "recall trial" refers to the CS+/CS+e and "maximum during acquisition" or "a CS+ trial" refers to the CS+/CS+e during acquisition (M.R. Milad, Ph.D., personal communication, September 26, 2018; K.G. Martinez, M.D., personal communication, September 26, 2019; B. Graham, Ph.D., personal communication, September 17, 2018; C. Hartley, Ph.D., personal communication, October 2, 2018; B. Hölzel, Ph.D., personal communication, December 5, 2018).

[b]Note that the sequence of the terms in the formula is different from other indices.

[c]Block defined as two subsequent CS+.

[d]The original publication refers to "CS+ trial" and "maximum CS+ responding during acquisition." In this study, "CS+ trial" refers to the CS+e and "maximum CS+ responding during acquisition" refers to the CS+e (M.R. Milad, Ph.D., personal communication, September 26, 2018).

[e]The formula reported in the original publication was spelled out incorrectly (M.R. Milad, Ph.D., personal communication, September 26, 2018).

[f]The formula (67) was each subject's average skin conductance responses during extinction recall were divided by their largest skin conductance response to the CS+ trials during conditioning. It was clarified by the authors that this refers to the first four CS+e trials during the retention test (despite the retention phase having eight trials in total) and that CS+ during conditioning referred to the CS+e only (M.R. Milad, Ph.D., and B. Graham, Ph.D., personal communication, October 30, 2018).

[g]The first trial of the re-extinction session was designated as a CS− to absorb the initial orienting response that commonly occurs at the start of the session, and was therefore disregarded before all day 2 analyses (27).

[h]Pair is defined as CS+ and its corresponding CS−.

[i]The Methods and Materials section does not indicate contextual manipulations but rather refers to a previous study (16) that did employ context changes.

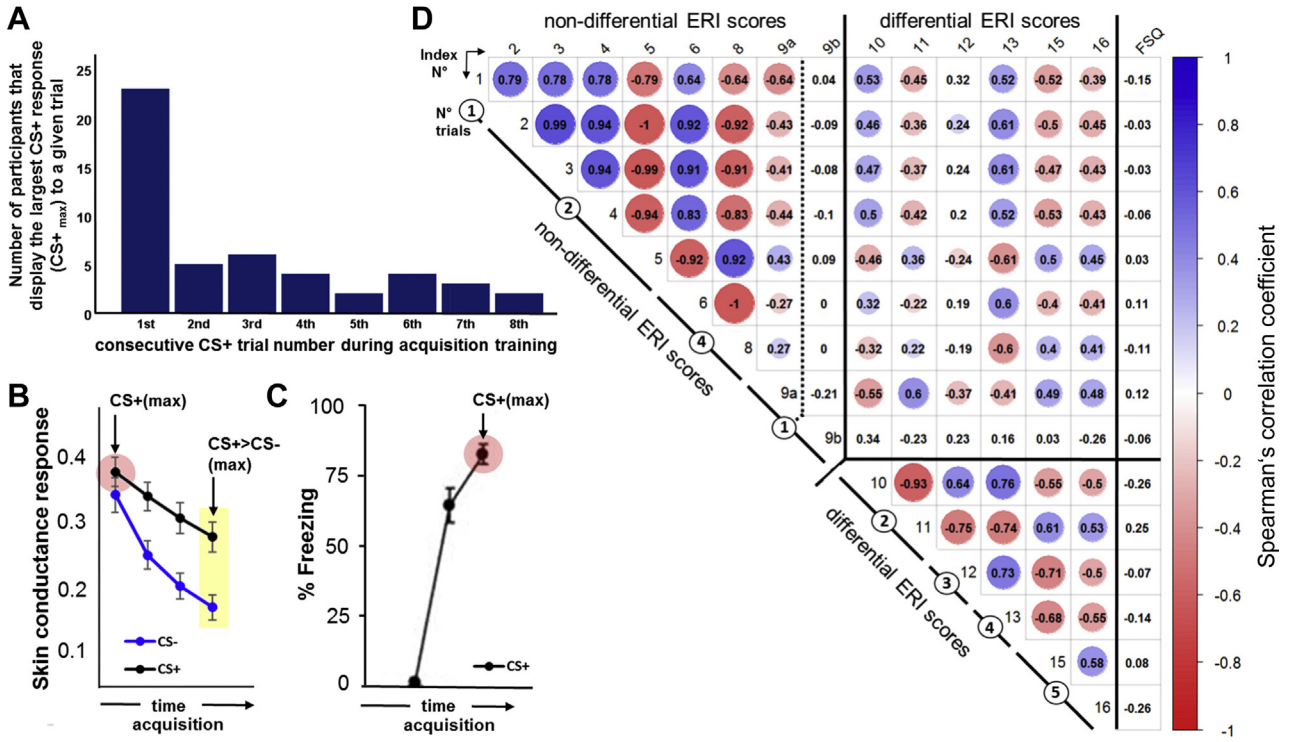

Figure 1. **(A)** Number of individuals in our dataset (from $N = 50$) that displayed the maximum conditional stimulus [CS+(max)] response to each of the eight CS+ trials during acquisition training. **(B)** Acquisition trials reflecting maximum responding to the CS+ (highlighted in red) as well as maximum differential responding (i.e., CS+ > nonconditioned stimulus (CS−); highlighted in yellow) in the present study in humans employing a differential conditioning protocol with 100% reinforcement (blocks of two trials shown; the outcome measure was skin conductance responding). **(C)** Acquisition trials reflecting CS+(max) response (highlighted in red) in a rodent study employing a single-cue conditioning protocol (blocks of two trials shown; the outcome measure was freezing). Modified with permission from Quirk (16) with permission from the publisher (copyright by Cold Spring Harbor Laboratory Press). **(D)** Correlation matrix (Spearman's *r*) between the different extinction retention index (ERI) formulas as derived from our systematic literature search (as indicated in Table 1) as well as the Fear of Spiders Questionnaire (FSQ) as recalculated based in our data (see above). Correlations are illustrated as a heatmap (blue: significant positive correlation; red: significant negative correlation; white cell: nonsignificant correlation [i.e., $p > .05$]) using the corrplot package in R. Correction for multiple comparisons was applied separately for the cross-ERI correlations and the correlation between the ERIs and the FSQ, respectively. Index 7 is not included in the correlation matrix, as it is identical to index 6 when calculated in our dataset because the dataset used for calculations did not include an extinguished and unextinguished CS+, but rather only a single CS+. Index 14 is not included here, as it is based on the difference between the extinguished and unextinguished CS+, which are not available in this dataset. We, however, refer to the Supplement for results of additional datasets (datasets 2–4) that employ these two different CS+ types (extinguished and unextinguished CS+) as well as a partial reinforcement rate and immediate (dataset 3) and delayed extinction training (dataset 2 and 4). The negative correlations between some of the ERIs (e.g., ERIs 5 and 8 and 9a) and the other nondifferential ERIs (i.e., ERIs 1–4 and 6) result from the fact that the latter subtract the retention score (i.e., responding during retention divided by responding during acquisition) from 100, which yields the percentage of fear not recovered (i.e., extinction retention), whereas ERIs 5, 8, and 9a reflect the percentage of fear recovered. While the interpretation of the score is thus the inverse, the sign of the correlation (i.e., positive or negative) is not of primary interest to our question and is ignored henceforward. Error bars show SEM.

differential responding between a pair of CS+ and CS− presentations is typically observed at the very end of acquisition training (illustrated in our data in Figure 1B). Hence, the maximum differential responding during fear acquisition training is more likely to relate to associative learning processes, as it would be the case for maximum freezing to the CS+ in rodents (see Figure 1B, right). Note, however, that only a few studies have employed differential responding during acquisition training to calculate the ERI (see Table 1).

Correlations Among ERIs

Correlations among the 16 identified ERIs in our dataset ranged from .003 to (−)1 (see Figure 1D; note that the algebraic sign will be ignored henceforward, as it only reflects the interpretation as % fear recalled or % fear not recalled). Overall, nondifferential and differential indices emerged as two distinct clusters (with the exception of the single CS− based index 9b), with correlations ranging between .27 and 1 within nondifferential ERIs and between .5 and .93 within differential ERIs. The correlations between differential and nondifferential ERIs ranged between .19 and .61. Results of the additional datasets show a similar pattern of correlations (see Supplemental Figure S2).

Correlations between ERIs and FSQ ranged between (−).03 and (−).26 (again, ignoring the negative algebraic sign), and all correlations between the FSQ and any of the ERIs were nonsignificant (see Figure 1D).

DISCUSSION

Precision in concepts, methods, and data analysis is key to science. By using the ERI as an example, we have illustrated

the problem of (often unrecognized) heterogeneity in operationalization for fear extinction retention research in humans. Awareness to these matters is an important first step (31) toward more rigor in the field and successful translation into clinical applications.

First, we have highlighted that the term "extinction retention" is often employed despite experimental designs not allowing inference of dominant recall of extinction memory (i.e., $A_{acq}A_{ext}A_{test}$ paradigm; see Table 1), which is misleading.

Second, from a procedural perspective, we show substantial variation in the calculation of an extinction retention index, with unsatisfactory correlations among the 16 different ERI versions across four datasets (20–22). Hence, we argue that the ERI, initially intended to be a cross-species translational measure, has evolved into a set of idiosyncratic formulas. This may hamper replicability and advancement in the field (32,33).

Third, from a conceptual perspective, we highlight below that none of the 16 different ERI formulas can be recommended as a good operationalization of the theoretical construct of extinction retention.

Does the ERI Make Sense From a Conceptual Perspective?

The rationale for the ERI is to express responding during a retention test as a percentage of responding during acquisition (29).

According to prevailing extinction theories (6,14), however, whether fear will reoccur at this later test (i.e., return of fear) or not (i.e., recall of extinction) is determined by the dominance of the fear memory over the extinction memory (or vice versa)—hence, it depends on both the fear memory and the extinction memory. Thus, it is surprising that most ERIs have controlled for responding during acquisition training, whereas control for extinction is very rare (and control for both has not been reported)—implying that extinction will be similarly efficient for all individuals. For instance, consider two individuals, X and Y, showing identical CS+ responding (0.5 μS) during the retention test after different amounts of maximum CS+ (CS+max) responses (1 μS vs. 0.5 μS) during acquisition training. Normalizing CS+ responses during the retention test for CS+(max) responding during acquisition training (i.e., index 1) would yield a 50% extinction retention for individual X [i.e., 100 − (100 × 1 μS/0.5 μS)] but 0% for individual Y [i.e., 100 − (100 × 0.5 μS/0.5 μS)], and we would infer better extinction in X than in Y. Moreover, not only the strength, but also the consolidation of fear and extinction memory acquisition are crucial for later retention. The major role of consolidation processes is illustrated by the fact that within-session extinction learning is not significantly correlated with between-session extinction learning (34) or performance at a later test in humans (35) or rodents (36–38). In our example, individuals X and Y may show an identical amount of CS+(max) responding (0.5 μS) during acquisition training but might undergo efficient or inefficient consolidation of fear memory, respectively. When these individuals show different amounts of CS+ responding (1.0 μS vs. 0.5 μS) during the retention test, the ERI (typically claiming to correct for acquisition performance) would, however, attribute these to the retention of extinction rather than to possibly different levels of consolidation of fear memory.

In sum, we argue that the theoretical foundation of the ERI to express responding at a retention test as a fraction of responding during fear acquisition training, as employed in most ERIs, does not map well onto prevailing theories and empirical findings. In addition, none of the ERIs showed a consistent association to measures of fear/anxiety across datasets (i.e., FSQ and State-Trait Anxiety Inventory). In fact, there was a consistency in the absence of such a relation.

Does the Operationalization of the ERI Make Sense?

Here, we identified 16 different operationalizations of the ERI, all intended to capture the same process (i.e., extinction retention), but empirically showing unsatisfactory correlations across four datasets. Importantly, although the four datasets used different procedures (e.g., immediate vs. delayed extinction training, CS+ vs. CS+e and CS+u), the pattern of correlations across ERIs is very similar across datasets. This highlights the robustness and generalizability of our findings. Of note, the nondifferential ERIs seem to be more related to each other than the differential ERIs are, probably indicating that there is less variability in the former than in the latter (e.g., ERIs 10 and 13 control for extinction retention with acquisition data, whereas ERIs 12 and 14 do not).

Importantly, the ERI has been translated from rodent freezing [e.g., (16)] to human work mainly using SCRs. Procedural differences between rodent and human work may, however, limit direct translatability of the ERI: rodent work employs mostly single-cue designs (i.e., CS+ only), while human work employs almost exclusively differential designs (CS+ vs. CS−). Remarkably, despite differential designs, most ERIs employed in humans are nondifferential (i.e., including CS+/CS+e only) (Table 1), which is problematic. First, the CS− was introduced to control for general responsivity and nonassociative processes such as arousal or orienting (13), and conditioned responding is typically quantified as differential (i.e., CS+ vs. CS−) responding. As such, the typical ERI calculations (e.g., mean CS+ responding during recall/CS+(max) responding during acquisition) may capture general arousal/orienting rather than associative processes. Second, CS+(max) responding during acquisition does not seem to reflect acquisition strength. As illustrated in Figure 1B, the maximum CS+ response during acquisition is most frequently observed in the first CS+ presentation preceding the first US presentation and therefore reflects orienting (30). To control for potential effects of this orienting response during extinction retention, some authors have established that the first trial during retention is always a CS− and disregarded this first trial in the calculations of the ERI [cf. (27)]. Importantly, in freezing, the CS+(max) typically occurs at the end of acquisition, illustrating the challenges and limitations of direct cross-species translation.

Similarly, SCRs to the first CS+ at retention test may primarily reflect orienting and arousal when considered in isolation (i.e., without comparing to the CS−). As a consequence, nondifferential ERIs cannot answer the question they intended to (i.e., "How much of the acquired fear comes back?").

Of note, while traditionally employed for SCRs, the ERI has recently been expanded to other outcome measures (i.e., fear-potentiated startle and ratings) (20,39–42). Importantly, the

conceptual problems we discuss in this work also apply to these other outcome measures. In addition, ERIs including correction for CS+(max) responding during acquisition are not widely applicable to functional magnetic resonance imaging data, as single-trial analyses in functional magnetic resonance imaging are inherently difficult. Consequently, studies using multiple outcome measures often employ an ERI for SCRs but base their critical calculations for other outcome measures on different calculations, rendering the results not comparable.

It is also important to note that different operationalizations of the ERI tap into different clinically relevant mechanisms. Patients have been shown to display deficits, particularly in extinction learning and safety signal (i.e., CS−) processing (23,24)—neither of which are accounted for in the current ERI operationalizations, in particular in nondifferential operationalizations.

In closing, we have exemplarily challenged both the conceptual foundations and procedural operationalization of extinction retention. While having a standardized way to quantify retention in an interpretable way is highly desirable, the complexity of processes, aims, and, consequentially, experimental designs in the field renders a simple gold standard solution impractical (13). Recommendations that can be derived from our work include 1) preferring differential responding over isolated CS+ responding; 2) refraining from employing CS+(max) responses during acquisition training as a measure of associative learning; and 3) appreciating the relevance of fear and extinction memory strength and their respective consolidation, which implies that correcting for one of these factors but not for the others will likely introduce a bias.

Here, we provide conceptual and empirical arguments that speak against the employment of an ERI, which leads to massive data reduction and hence interpretation problems. Rather than using an ERI, we suggest relying on within-session (i.e., retention test) differential responding rather than merely CS+ based responses. Furthermore, we suggest considering the dynamics over time (13,43) and providing trial-by-trial data (whenever possible) for all stimuli and phases included in the experimental design (i.e., CS+ or CS+e/CS+u and CS−) as well as for all outcome measures. Other general recommendations, such as justifying the exclusion of participants and demonstrating the invariance of the results regarding exclusions if employed (13,44), as well as the use of hierarchical models over traditional analyses of variance (45), apply here as well. Yet, specific analysis choices that may depend on the specific design, such as the number of trials included/excluded, still need to be justified and reported in a transparent way.

Finally, raising awareness to the threat of (unrecognized) methodological and data analytical heterogeneity will hopefully 1) spark similar approaches in other subfields of fear conditioning research and beyond (see Supplemental Figure S3 for guidance), 2) increase rigor in reporting and analysis in the field, and 3) help extinction (retention) research to resume the path for becoming "one of the best opportunities for translating neuroscience discoveries into clinical applications" (1).

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ARTICLE INFORMATION

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