The Effects of Extinction in Multiple Spatial Contexts on Fear Recovery in Animals and Humans: a Meta-analysis Protocol

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Protocol

Abstract

Background

Laboratory studies that utilise an exposure-based approach seek to reduce recovery through repeated nonreinforced presentations of a fearful or appetitive stimulus. A recent meta-analysis on post-retrieval extinction revealed small and non-significant effects on fear recovery. While meta-analyses on the use of pharmacologic agents revealed promising results, deploying such methods as first-line treatment for anxiety disorders is not practicable. To date, there has not been a systematic review or meta-analysis conducted to evaluate the overall effectiveness of laboratory-based multiple spatial context extinction on fear renewal in animals or humans. The present paper provides a protocol for a systematic review and meta-analysis to synthesise current literature investigating fear extinction in multiple spatial contexts. This will help provide information into the types of circumstances required to effectively implement this manipulation as a clinical treatment for anxiety-based disorders.

Methods

A literature search will be conducted on electronic databases with the addition of forward and backward reference checking. Only primary research empirical studies that investigated fear conditioning and manipulated extinction training over two or more spatial contexts will be included. Eligible studies must include at least one control group that received comparable extinction in one context. The population of the studies will include both human (non-clinical) and non-human animals (e.g. rats). There will be no limitations on publication date, country of origin, or language. Essential scores related to recovery will be recorded. Data will be extracted by one of the two reviewers and quality of studies will be assessed by both the Cochrane Risk of Bias tool version 2, for studies with human participants and the Systematic Review Centre for Laboratory Animal Experimentation risk of bias tool, for studies with animals. A three-level meta-analysis will be conducted to determine fear attenuating effects of extinction across multiple spatial contexts. Should moderate-high heterogeneity be found, causes will be investigated through subgroup analyses.

Discussion

The planned review will be the first to present a comprehensive evaluation of the current state of the effectiveness of conducting multiple spatial context extinction on the possible attenuation of conditioned fear. The review will determine the types of circumstances that may provide better efficacy into informing translational research into clinical exposure therapy for anxiety-based disorders.

Systematic review registration

PROSPERO 142518, edited on 30th Oct 2020, pending approval.

Background

Relapse after treatment is a common occurrence in many psychological disorders. This is particularly prevalent for anxiety disorders. The frequent relapse of these conditions leads to a high global burden of disease ranking (1). Therapeutic modalities for these conditions have utilised extinction as a component in their treatment. In anxiety disorders, fear reduction may be achieved through repeated nonreinforced presentations of a fearful stimulus. These exposure techniques are analogous to laboratory extinction procedures in learning theory. However, the occurrence of relapse suggests that extinction learning may not have successfully inhibited previous conditioned behaviour.

In learning theory, recovery from extinction is analogous to relapse. Recovery is observed when an extinguished conditioned behaviour returns. There are several forms of recovery from extinction including:

1. *Spontaneous recovery* – the extinguished behaviour returns after a period of rest is introduced after extinction (2).
2. *Renewal* – the extinguished behaviour returns in a context other than the one in which extinction training took place (3).
3. *Reinstatement* – the extinguished behaviour returns when the organism experiences the unconditional stimulus (US) after extinction (4, 5).

The recovery phenomena meant that patients undergoing clinical exposure-based therapies may be inherently vulnerable to relapse as extinction is not permanent. Researchers thus sought to mitigate recovery effects by weakening the conditioned stimulus-unconditioned stimulus (CS-US) associations. These include reconsolidation interference via pharmacological interventions (e.g., 6) and post-retrieval extinction (e.g., 7, 8), and extinction across multiple spatial contexts (e.g., 9, 10).

Meta-analyses reviewing partial glutamatergic N-methyl D-aspartate (NMDA) agonists across animal and human studies (e.g., 11) and human studies (e.g., 12), and NMDA and beta-adrenergic receptor antagonists in animal studies (e.g., 13) and human studies (e.g., 14) have shown promising results in attenuating fear and appetitive memories. However, the use of pharmacological agents as first-line treatment in anxiety disorders is not standard clinical practice (7, 11). A meta-analysis combining both animal and human studies on post-retrieval extinction on reconsolidation reported a significant and large effect (g = 0.89) in attenuating appetitive responses in animals (15). However, targeting original fear memory was less effective with a significant and small-to-moderate effect (g = 0.40) in humans, and a non-significant and small effect (g = 0.21) in animals (15).

Another exposure-based technique involves conducting extinction training across multiple spatial contexts. Gunther, Denniston (9) were the first to demonstrate this technique. In their first experiment, rats received excitatory pairings between a CS and an aversive US in a single context. Then they underwent extinction training in either one or three new contexts. When tested for ABC renewal, that is, tested in a novel context, rats that experienced extinction over multiple contexts displayed lower levels of renewal

(i.e., recovery) compared to those that experienced extinction in one context. This result has been replicated in rats (e.g. 16, 17), and humans (e.g., 10, 18).

Despite the observation of reduced renewal following extinction in multiple contexts, there are inconsistencies in the findings. Bouton, García-Gutiérrez (19) did not find a reduction of renewal in rats after conducting extinction in three different contexts. These results were corroborated by Thomas and colleagues' first experiment, which similarly found no significant impact of multiple context extinction in rats (20). However, their second experiment found a significant reduction in renewal if extinction was conducted over multiple contexts and augmented by increasing the number of nonreinforced trials. In humans, the results also appear to be inconsistent. Neumann (10) observed an abolishment of renewal when extinction was conducted over multiple contexts in a conditioned suppression task. However, a later study found no significant effect of this manipulation in a shock expectancy procedure (21).

To determine the manipulations that facilitate the effective reduction of recovery effects through multiple spatial context extinction, there is a need to review the state of current literature and establish the overall efficacy found to date. Furthermore, due to the translational goals of this review, both animal and human studies will be evaluated. Moreover, the extent to which recovery is attenuated relative to a control group (i.e., the effect size) has not been analysed. This review aims to provide a comprehensive synthesis and analysis of the available evidence regarding this form of extinction enhancement. This will provide information on the efficacy of this manipulation for future translational research into improving clinical treatment through exposure therapy.

Objectives

The objective of this review is to evaluate the effectiveness of extinction when conducted in multiple spatial contexts. The review will synthesise and summarise all current studies that utilised multiple spatial contexts extinction manipulation to reduce fear renewal effects. The review will also compare the effects of extinction in multiple spatial contexts between animals and non-clinical human participants (e.g., 11, 15).

Methods/design

This systematic review protocol has been developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and the Cochrane Checklist of items to consider in data collection or data extraction (additional File 1). The review protocol has been registered a priori at the International Prospective Register of Systematic Reviews (PROSPERO ID: 142518).

Eligibility Criteria

Population

The review will include mammalian animal subjects (e.g., rats and mice) and non-clinical human participants. Studies that use pre-clinical human participants (e.g., preexisting and undiagnosed fear of spiders or heights) or clinical samples (i.e., patients with mental health diagnoses) will not be included as these studies do not include a fear conditioning procedure and employ exposure therapy as the intervention.

Interventions

The review will include experiments investigating extinction training in multiple spatial contexts. There are no restrictions to the timing, extent, duration, reinforcement schedule, use of a control stimulus (e.g., CS-), combination of interventions (e.g., multiple spatial contexts and massive extinction; see 22), and administration of nonreinforced trials within each set of extinction training. Critically, the intervention must aim to reduce conditioned fear in animals or humans. Studies that do not conduct fear conditioning prior to extinction will not be considered.

Comparators

All included studies must have at least one control group that received comparable extinction treatment in one spatial context. These studies must also have outcome measures similar to their respective comparison groups. Furthermore, comparison groups should comprise of samples within the same population. Any study that does not utilise such procedures in the control group will be excluded.

Outcome measures

All studies must contain at least one measurement of fear recovery by testing either spontaneous recovery, renewal (ABA or ABC renewal), or reinstatement after extinction training. For studies with non-clinical human samples, dependent variables include skin-conductance responses, heartrate, conditioned suppression, fear-potentiated startle responses, and US expectancy. Outlying dependent variables not listed above will be considered and fully discussed. For animal studies, conditioned suppression and suppression ratio will be reported. Data from studies that conduct progression of fear recovery (e.g., fear renewal followed by spontaneous recovery) will be included and statistical methods (e.g., three-level meta-analysis) will be used to account for the dependence of effect sizes within groups. A summary of findings table will be generated to highlight the main outcomes for informing future translational research into exposure therapy conducted in clinical settings.

Study designs

The review will include laboratory-based primary research empirical studies. Subjects and participants must be randomised. All studies must, in a sequential order, contain a fear conditioning procedure, followed by manipulating extinction training with a direct impact on the conditioned response conducted across two or more spatial contexts, and test of recovery of the conditioned response. Fear conditioning is defined as pairing a neutral stimulus (e.g., tone) with a behaviorally relevant fearful stimulus (e.g., mild

electric shock). Extinction across multiple spatial contexts is defined as receiving a set of extinction training in one environment, followed sequentially by receiving another set of extinction training in a different environment. An environment can be defined as a physical (e.g., 19), digital (e.g., 23), or virtual (e.g., 24) space, housed within the same locale (e.g., 10) or across different locations (e.g., 25), and can differ in dimensions, appearance (e.g., colour, lighting, patterns, and texture), and odour.

Language of publication

There will be no limitations on publication date, country of origin, or language. However, only search terms in the English language will be used (e.g., Spanish search terms will not be used). For articles published in other languages, language translation assistance will be sought within James Cook University Singapore and the National University of Singapore. If no translators are available, Google Translate® will be used to convert the article to English.

Exclusion criteria

Studies that did not conduct fear conditioning prior to extinction will not be considered. Studies that did not conduct experiments (e.g., reviews) will not be included. Studies that investigate extinction across multiple temporal contexts (e.g., 26), extinction using multiple target and partner cues (e.g., 27), extinction-based exposure therapy (e.g., 28), cue or outcome interference (e.g., 29), reconsolidation blockade via drugs (e.g., 30) or reconsolidation blockade via extinction (e.g., 7) will not be included in this review. However, studies that use a combination of techniques, such as reconsolidation blockade and extinction in multiple spatial contexts, will be considered. Clinical studies will not be included due to the complexities of exposure therapy which embeds learning mechanisms such as psychoeducation and relaxation.

Information sources and search strategy

A comprehensive search with no restrictions on language will be conducted on PubMed, PsycINFO, Web of Science and Scopus for peer-reviewed studies on extinction in multiple contexts in animals and humans with the phrase:

(((((multiple context extinction) OR (multiple contexts extinction)) OR (extinction in multiple contexts)) OR (extinction across multiple contexts)) OR (multiple AND contexts AND extinction). Search details such as date, location, and method will be recorded, and search results will be illustrated in a PRISMA flow diagram. Hand-searching will be done through forward and backward searching of references in eligible studies. Authors will be contacted to request for unpublished data.

Data management

Two independent reviewers will conduct the study selection. Studies identified through the search strategy will be extracted into a reference management software, EndNote (https://endnote.com/). The software will be used to filter duplicate studies which will then be manually checked by one reviewer to ensure any remaining duplicates are removed and quarantined.

Selection process

This will consist of a 2-step title and abstract screening and full-text review process. The first screening process will begin with both reviewers independently conducting a screening of the titles and abstracts. This will ensure that each article gets screened by two reviewers. The list of identified articles for full-text screening will be contrasted and deliberated between the two reviewers. Following this, both reviewers will independently conduct full-text screening of a split of selected articles to determine inclusion. In addition, hand-searching will be done through forward and backward searching of references in individual studies. Both reviewers will need come to a consensus on the final list of included articles.

Data collection process

One reviewer will independently extract data from the list of identified articles. The data extracted will be reviewed by the second reviewer and discrepancies will be discussed before reaching a consensus. Data extraction will be piloted on a small number of identified studies. Information will be extracted onto a Microsoft Excel® sheet and include general article information (first author, year, title); aim of experiment (experiment number, objectives, outcomes, type of experiment); study population (species, type of sample, total sample, number of groups, sample size per group, mean age); study design (experimental paradigm, recovery mechanism, types of stimuli, types of contexts, counterbalancing strategies, context equalisation, context exposure, context preexposure, number of acquisition, extinction, and test contexts, trial duration, intertrial interval, interstimulus interval, retention interval); outcome measurement (conditioned suppression, conditioned suppression ratio, skin-conductance response, heartrate, US expectancy). Authors will be contacted via email to request for data clarifications or unpublished data. Requests to authors will be followed-up twice and the article will be rejected if the author does not reply within 1 month of the initial email.

Assessment of risk of bias in included studies

The full range of studies involving manipulation of multiple extinction contexts involves animals and humans. Two tools will be used for evaluation of the risk of bias. The Cochrane Risk of Bias tool version 2 (RoB 2) will be used to evaluate risk of bias in all human studies (31). RoB 2 assesses bias on five domains – randomisation process, deviation from intended intervention, missing outcome data, measurement of outcome and selection of the reported result. The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) will be used as the RoB tool for all animal studies included

in the review. The SYRCLE assesses for potential issues with selection bias, performance bias, detection bias, attrition bias and reporting bias (32). Each study will be evaluated by the appropriate RoB tool by the first reviewer and evaluated by the second reviewer. Discrepancies will be discussed before reaching a consensus. The quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Data synthesis

Narrative synthesis

A narrative synthesis of the findings will be provided. This will include the type of measure used to determine recovery from extinction, the conceptualisation of contexts and study-specific manipulation of different contexts, the type of conditioned response undergoing extinction, and species.

Quantitative synthesis

It is anticipated that the variation of data analysis would vary widely across studies. Hence, following precedent literature (15), effect sizes will be based on 1) within-group differences in fear between the last extinction trial to the first test; 2) after between-group differences in fear have been shown to be nonsignificant, followed by observing recovery at test. In the event where a study employs both types of analyses, the first method will be used. For binary outcomes, a standard estimation of risk ratio (RR) and its 95% confidence interval (CI) will be used, and studies that use odds ratios (OR) will be transformed to RRs. The RR summary statistic is chosen as it is deemed more intuitive than ORs (33), and ORs are regarded as relative risks across clinical trials (34). For continuous outcomes, means, standard deviations, F tests, p- and t-values will be used. t-tests will be assumed to be two-sided unless specifically reported to be one-sided. Significance values will be assumed to be $p = .05$ unless specifically reported otherwise. Analyses will be conducted using the Review Manager (RevMan 5) tool. To account for the small sample sizes across studies, Hedges' g will be used as a measure of effect size (35), where small, moderate, and large effects fall within 0.2, 0.5 and 0.8 respectively (36). A three-level meta-analysis will be conducted to account for studies that conduct progression of fear recovery (e.g., fear renewal followed by spontaneous recovery) that result in multiple effect sizes from the same sample (37–40; e.g., 15). Aggregate effect sizes will be calculated separately for animal fear conditioning studies, and non-clinical human fear conditioning studies. In addition, aggregate effect sizes will be calculated for each and all (combined) recovery outcomes (i.e., renewal, spontaneous recovery, reinstatement) to ascertain the efficacy of multiple spatial contexts extinction for each recovery type.

Assessment of statistical heterogeneity

Heterogeneity will be evaluated using the Q statistic and I^2 statistic: the Q statistic detects the presence of heterogeneity where a significant Q statistic value suggests a presence of heterogeneity, while the I^2 statistic calculates the extent of heterogeneity whereby I^2 values of 25%, 50% and 75% indicate a low,

moderate, and high heterogeneity respectively. Further prespecified subgroup analyses (see Table 1) will be conducted if moderate heterogeneity is detected to assess the influence of moderators.

Table 1
List of potential subgroups

	Characteristics	Subgroups
1	Species	Humans / Animals
2	Context Conditioning Design	ABA / ABC

Publication bias

Following the recommendation of the Cochrane handbook for systematic reviews of interventions, publication bias will be assessed if an outcome contains at least 10 studies (41). Eggers' test of intercept will be used to assess the existence of asymmetry, and therefore publication bias, in a funnel plot (42).

Discussion

This will be the first systematic review and meta-analyses conducted to evaluate the current efficacy of extinction treatment over multiple spatial contexts. The review will ascertain the inter-species reaction to experiencing multiple contexts and whether this form of manipulation attenuates recovery from extinction. Moreover, it will inform researchers on whether the effects observed in non-human animal studies are consistent and similar with the results observed in human research. Several limitations will be expected while conducting this review. For instance, the varying design parameters (e.g., retention intervals, intertrial intervals) and study designs (e.g., lever press versus head poke operant procedures) between studies will make the analysis of results difficult and may affect the search parameters. To overcome these limitations, in cases of moderate-high heterogeneity, causes will be investigated through subgroup analyses, and search strategies will include hand-searching through identified articles. This review will also report the knowledge strengths and gaps pertaining to the research objectives. Findings of this review will be reported through peer-reviewed academic publications and conference proceedings and inform the public on the conditions that may be relevant to conduct this form of exposure successfully. The importance of this review lies in the potential for informing future translational research into exposure therapy conducted in clinical settings.

Abbreviations

- CI – confidence interval
- CS – conditioned stimulus
- GRADE – Grading of Recommendations Assessment, Development and Evaluation

- NMDA – N-methyl D-aspartate
- OR – odds ratio
- PRISMA-P – Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
- PROSPERO – International Prospective Register of Systematic Reviews
- RevMan – Review Manager
- RoB – risk of bias
- RR – risk ratio
- SYRCLE – Systematic Review Centre for Laboratory Animal Experimentation
- US – unconditioned stimulus

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The manuscript was drafted by WAV with input from MBL. MBL first conceived the idea and WAV initiated the project. MBL provided input and training on data analysis aspects. CWM amended the background, methods, data synthesis and discussion sections outlined in the manuscript and will be conducting the

review in collaboration with MBL. MBL is the guarantor of this review. All authors have contributed to the methodological development. All authors have read and approved the final manuscript.

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