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A Comparison of the Relative Magnitude of Combinations of Relapse Types in Rats

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By

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Abstract

Applied behavior analysis uses scientifically derived methods to create treatments for socially significant behaviors. A threat to these successful treatments is the recurrence of previously reduced behavior (i.e., relapse). Relapse can be categorized into several types depending on the variables that induce relapse. Three types prevalent in clinical settings are reinstatement (i.e., induced by re-exposure to reinforcers or stimuli paired with the target behavior), renewal (i.e., induced by changes in context), and resurgence (i.e., induced by worsening of alternative reinforcement). Because relapse is harmful to long-term treatment maintenance, prior research has developed and tested mitigation strategies for these relapse types, largely beginning with basic/translational studies. Recent studies have found that pairwise combinations of these relapse types generally produce larger magnitude (i.e., the increase in count or frequency of target behavior between extinction and relapse) effects compared to traditional single-type relapse effects. Thus, some have called for the creation of mitigation strategies that target relapse types in combination. The present study presents a translational model for evaluating relapse induced by combinations of events to better simulate the effects that practitioners may face (i.e., multiple relapse types in combination), and to compare the relative magnitude of relapse between different combinations of relapse types. Four groups of rats were exposed to pairwise combinations of reinstatement, resurgence, and renewal conditions, as well as a three-way combination of all conditions. Relapse occurred and was similar in magnitude for all groups. Clinical implications, theoretical implications, and suggested future research are discussed.

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I want to specifically recognize and thank my parents. I dedicate my success and this project to them. Making them proud is my motivation for everything I have accomplished. I am forever grateful.

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Applied behavior analysis (ABA) uses methods derived from scientifically established principles of behavior to create treatments that benefit individuals in socially significant ways (Cooper et al., 2020). One way ABA benefits the individuals it serves is by implementing behavioral treatments to decrease the occurrence of dangerous or undesirable behavior such as property destruction (e.g., Bostow & Bailey, 1969; Fisher et al., 2020; Foxx & Meindl, 2007), aggression toward others (e.g., Falcomata et al., 2013), self-injurious or self-destructive behaviors (e.g., Azrin et al., 1982; Banda et al., 2009; Miltenberger et al., 1998; Smith et al., 1993), and substance abuse (e.g., Silverman et al., 2011). ABA treatments are often effective at decreasing these behaviors. However, relapse, the recurrence of behavior after its reduction in treatment, is a frequent threat to the successful generality and maintenance of treatment effects (e.g., Falligant et al., 2022; Kimball et al., 2023; Shahan, 2020).

Relapse can be categorized into distinct types specific to the variables that occur during or after treatment. Though there are many types of relapse, three types that may be particularly relevant for behavior reduction plans implemented in ABA clinics are reinstatement, renewal, and resurgence (Kimball et al., 2023). Reinstatement occurs when stimuli or reinforcers previously associated with the undesirable behavior are reintroduced after the reduction or elimination of the behavior (Falcomata et al., 2013; Miranda-Dukoski et al., 2016). Reinstatement can occur in clinical settings due to errors in treatment delivery like caregivers delivering reinforcement contingent on problem behavior (Kranak et al., 2012; Pritchard et al., 2014), or a client receiving attention from a staff member when the problem behavior was previously attention-maintained (Falcomata et al., 2013). Renewal is induced when clients are exposed to contexts that differ from the treatment context, such as the original context in which

problem behavior was reinforced, or new contexts (Kimball & Kranak, 2022). This often occurs when a client is present in a setting (e.g., home, school) other than the treatment setting (e.g., an ABA clinic). Problem behavior can be dangerous, and treatment in a clinical setting is sometimes preferred for safety and high levels of treatment control. However, if treatment effects do not generalize to other contexts, clients are at risk of renewal when they leave the clinical setting (Petscher et al., 2009; Podlesnik et al., 2017). Resurgence is induced by worsening of reinforcement conditions for an alternative behavior (Bouton et al., 2012; Kincaid et al., 2015). Resurgence is common in widely used differential reinforcement procedures (e.g., functional communication training) due to the accidental or planned reduction or removal of reinforcement for alternative behavior. Resurgence may occur when conditions of reinforcement for alternative behavior worsen. This can occur during transitions from dense to lean schedules of reinforcement or increases in response requirements for reinforcement delivery (Briggs et al., 2018; Kimball et. al., 2023). Each of these relapse types threatens the long-term maintenance of effective treatment and suggests the need to develop methods to reduce or mitigate relapse to increase the lasting success of treatment (Kimball et al., 2023).

Several types of relapse-type-specific mitigation strategies have been developed to address relapse following behavior reduction. Examples include increasing treatment fidelity among staff or reducing omission errors in treatment delivery to reduce reinstatement (Kimball et al., 2023), training in multiple contexts to reduce renewal (Podlesnik et al., 2017), and cycling between differential reinforcement of alternative behavior (DRA, i.e., placing a target behavior on extinction and reinforcing an alternative behavior) and extinction to reduce resurgence (Fisher et al., 2020). These relapse mitigation strategies tend to be effective at reducing the type of relapse they target but may have limited utility for other relapse types (Kimball et al., 2023).

While existing mitigation techniques may be effective when the correct relapse type was anticipated and occurs in isolation, behavior reduced in the clinic may encounter any combination of events known to induce relapse (e.g., accidental reinforcement, changes in context, worsening of alternative reinforcement). This potential for any combination of relapse-inducing events complicates selection of appropriate mitigation strategies. As such, some have suggested simultaneous implementation of multiple relapse mitigation strategies (e.g., Kimball et al., 2023; Mitteer et al., 2021; Podlesnik, 2018). While this is likely the most effective way to reduce relapse at present, implementing several mitigation techniques may not be feasible due to time constraints placed on clinicians (see LeBlanc et al., 2019), and could negatively affect treatment (Kimball, et al., 2023). For example, implementing and planning several relapse mitigation strategies is time consuming for practitioners, leaving less time available for skill acquisition and other socially significant areas of treatment. Relatedly, it may also be difficult to determine what events or combinations of events induced relapse effects observed in clinical situations. Altogether, programming or combining multiple relapse mitigation techniques could be cumbersome at best, and inaccurate or harmful at worst.

Another complication with current relapse mitigation techniques is that they have not been widely tested in situations involving combinations of relapse-inducing events in the clinic. This lack of testing is important because prior work, mostly translational studies with non-human animals, has sometimes found increased relapse magnitude (i.e., the increase in count or frequency of target behavior between extinction and relapse) following the co-occurrence of relapse inducing variables (Kincaid et al., 2015; Liggett et al., 2018; Wathen & Podlesnik, 2018; but see, Bouton & Trask, 2016; Sweeney & Shahan, 2015). For example, Kincaid et al., (2015) showed that context changes (i.e., renewal) combined with worsening in alternative

reinforcement (i.e., resurgence) produced a greater degree of relapse of key pecking in pigeons than either renewal or resurgence alone. Further, increases in behavior induced by renewal and resurgence may also increase chances of accidental reinforcement, leading to reinstatement of problem behavior (Liggett, et al., 2018; Mitteer et al., 2021). Thus, combinations of relapse-inducing events may lead to greater magnitude of relapse effects and increase chances of other types of relapse. Lastly, most research examining relapse effects induced by combinations of relapse-inducing events have focused only on pairwise combinations. This is problematic because clinically relevant behavior may be susceptible to any combination of relapse-inducing events. Altogether, this potential for increased relapse magnitude and relapse susceptibility have led to recent calls for more research into relapse induced by combinations of relapse-inducing events (e.g., Falligant et al., 2022).

Much of the foundational knowledge about relapse and relapse-mitigation strategies has been developed in the basic and translational literature using human or non-human animal operant procedures. This is likely due to the avoidance of increased socially significant problem behavior and improved experimental control afforded by basic lab preparations. Indeed, many existing relapse mitigation strategies were first developed in translational experiments (e.g., multiple-context training, Bernal-Gamboa et al., 2017b; cycling alternative reinforcement availability, Shahan et al., 2020). A translational animal model of combined relapse types is warranted given the success of past translational efforts toward relapse mitigation, the current need for strategies to reduce relapse induced by combinations of relapse-inducing events, and the difficulty in determining which events led to relapse in clinical situations. Such a model would allow evaluations of the efficacy of relapse mitigation techniques for combined relapse-inducing

events and increase the face validity of animal models used for translation to clinically relevant relapse effects.

The primary goal of the present research is to develop a translational model of relapse generated by combined relapse-inducing events. A secondary goal is to determine the relative magnitude of relapse effects generated by different combinations of relapse-inducing events. Knowing what combinations of events produce the largest magnitude of relapse may help clinicians focus relapse mitigation efforts on the most impactful relapse types, alleviating some concerns of time constraints. To these ends, four groups of rats received reinforcement for pressing a target lever before target responding was extinguished and relapse was induced. Reinstatement was induced by providing response-dependent stimuli that were available during baseline, but not extinction, as well as one response-independent reinforcer. Renewal was induced by removing rats from the extinction context (i.e., Context B) and returning them to the context present during baseline (i.e., Context A) while continuing extinction conditions (i.e., ABA renewal). Resurgence was induced by removing reinforcement for an alternative lever press that was available during extinction. The four groups of rats experienced combinations of events that induce reinstatement and renewal, reinstatement and resurgence, renewal and resurgence, or reinstatement, renewal, and resurgence.

Methods

Subjects

Sixteen experimentally naïve male Sprague Dawley rats (Charles River, Portage, MI), approximately 65 days old at the beginning of the experiment, served as subjects. Rats were pair-housed in a climate-controlled colony under a 12:12 light/dark cycle (lights on at 7 a.m.). Rats were maintained at 85% of their free feeding weights by post-session feeding and had free access

to water in their home cages. Approval for animal housing, care, and experimental procedures, was obtained by Jacksonville State University's Institutional Animal Care and Use Committee prior to experimentation (see Appendix A). The rats were separated into four groups: a combination group exposed to the events known to induce each of the three relapse types (i.e., Reinstatement + Renewal + Resurgence) and a group for paired combinations of each type (i.e., Reinstatement + Renewal, Renewal + Resurgence, and Reinstatement + Resurgence). One rat was excluded from the Reinstatement + Renewal + Resurgence group because it failed to acquire alternative responding.

Apparatus

The study used 16 identical Med Associates (St. Albans, VT) operant chambers measuring 30 cm x 24 cm x 21 cm and housed in light-and-sound attenuating cubicles. The chambers consisted of two side panels and a ceiling made of Plexiglas. On the front wall was an aluminum response panel equipped with two retractable levers below stimulus lights. Centered on the front wall and between the two levers was an aperture for delivery of 45-mg grain-based Dustless Precision Pellets (i.e., food; Bio-Serv, Flemington, NJ), which served as reinforcers. All reinforcer deliveries were followed by a 3 s blackout during which levers were retracted. A house light centered at the top of the front wall provided general chamber illumination. All sessions throughout were 30-min exclusive of food deliveries. For rats in groups with a renewal component (see below for group procedural details), contextual components consisted of either white paper with black dots lining the exterior Plexiglas walls, a small container with three drops of lemon essential oil placed inside the cubicle, and a black vinyl cover over the grid floor, or white paper with black stripes lining the exterior of Plexiglas walls, a small container with three drops of peppermint essential oil placed inside the cubicle, and a wood vinyl cover over the grid

floor. Contextual stimuli were counterbalanced across rats throughout phases to control for potential confounds of stimulus properties, and to reduce the likelihood of these stimuli signaling contingency changes for other groups (e.g., olfactory stimuli detectable in surrounding chambers). Rats with a reinstatement component also received simultaneously a 3 s, 2.9 kHz tone and a 3 s illumination of a stimulus light upon delivery of some reinforcers as detailed below.

Procedure

Pretraining

Pretraining began with two sessions of magazine training consisting of food delivery according to a variable time (VT) 60 s schedule for all rats (every 60 seconds, on average, a food pellet was delivered). The VT schedule and all variable-interval (VI) schedules described below were constructed of 10 intervals derived from the Flesher and Hoffman (1962) constant-probability distribution. Then, two sessions of AutoShaping were implemented (e.g., Sutton et al., 2021). That is, VT 50 s intertrial intervals were followed by insertion of the target lever for 10 s. Presses to the lever during these 10 s produced the reinforcer immediately according to a fixed ratio (FR) 1 schedule (a reinforcer is delivered contingent on every response). If the lever was not pressed during these 10 s, a food pellet was delivered response-independently, and the lever retracted. Target and alternative levers were left-right counterbalanced across rats. Then, rats began two sessions of an FR 1 schedule and response requirements increased for each of the following sessions according to the following progression: FR 1, FR 3, FR 5, FR 7, FR 10. Following FR training, rats experienced a VI schedule (reinforcement was delivered for the first response following a varying amount of time). This consisted of a VI 10 s schedule and increased in following sessions to a VI 15 s and VI 20 s schedule. Pretraining ended once

responding was visually stable (i.e., no increasing or decreasing trends) under VI 20 s reinforcement. The mean rate of target responding of total sessions for all rats in pretraining was 28 responses per minute.

Baseline

Prior to implementing Baseline, rats were divided into groups matched on Pretraining response rates. Beginning in Baseline, both levers were inserted at the beginning of each session. During Baseline, target lever responses produced food according to a VI 20 s schedule for all groups. A 3 s tone and illumination of a stimulus light above the target lever simultaneously occurred when reinforcement was delivered for groups with a reinstatement component. Context A stimuli were present in the chambers for groups with a renewal component. The Reinstatement + Renewal group received reinforcers and cues, and Baseline sessions took place in Context A. The Reinstatement + Resurgence group received reinforcers and cues for the target lever; no reinforcers were provided for the alternative lever. Baseline sessions took place in Context A for the Renewal + Resurgence group and no reinforcers were provided for the alternative lever. The Reinstatement + Renewal + Resurgence group received reinforcers and cues for the target lever, no reinforcers for the alternative lever, and Baseline sessions took place in Context A. Table 1 provides a summary of conditions for each group across the experiment.

Table 1

Conditions for All Groups Across Phases

Group	Baseline[A]		Extinction[B]		Relapse Testing[A]	
	Target	Alt	Target	Alt	Target	Alt
Reinstatement + Renewal*	VI 20 s + Cue	EXT	EXT	EXT	VI 20 s[$]	EXT
Reinstatement + Resurgence	VI 20 s + Cue	EXT	EXT	VI 20 s	VI 20 s[$]	EXT
Renewal + Resurgence*	VI 20 s	EXT	EXT	VI 20 s	EXT	EXT
Reinstatement + Renewal + Resurgence*	VI 20 s + Cue	EXT	EXT	VI 20 s	VI 20 s[$]	EXT

Note: [A] Indicates context A stimuli were in place, and [B] indicates context B stimuli were in place for groups including a renewal component (indicated by *). Cue indicates that reinforcer delivery was accompanied by a 3 s illumination of the stimulus light above the lever and a 3 s tone. Target = Target lever. Alt = Alternative lever. EXT = Extinction. VI 20 s indicates reinforcers were delivered according to a VI 20 s schedule. [$]Indicates a 3 s presentation of tone and stimulus light above the target lever, but no reinforcer delivery.

Extinction

During Extinction, target lever responses did not produce reinforcement for any group. Groups with a renewal component had Context B stimuli in place. For groups with a resurgence component, alternative lever responses produced reinforcement according to a VI 20 s schedule (see Table 1). The Reinstatement + Renewal group did not receive reinforcers or cues for the target lever, and Context B was in place for Extinction sessions. The Reinstatement + Resurgence group did not receive reinforcers or cues for the target lever but did receive reinforcers for the alternative lever according to a VI 20 s schedule. The Renewal + Resurgence group received reinforcers for the alternative lever according to a VI 20 s schedule and Context B was in place for Extinction sessions. The Reinstatement + Renewal + Resurgence group did not receive reinforcers or cues for the target lever, Context B was in place for Extinction sessions, and the alternative lever was reinforced on a VI 20 s schedule.

Relapse Testing

For all groups in Relapse Testing, responses to neither lever produced reinforcement. For groups with a reinstatement component, the stimulus light above the target lever was illuminated for 3 s, a 3 s tone was delivered, and a single food pellet was delivered response-independently at the beginning of the session. Then, the target lever produced 3 s of illumination of the stimulus light above the target lever and a 3 s tone according to a VI 20 s schedule, as in baseline. Food was not delivered for the remainder of sessions for any rats. For groups with a renewal component, Context A stimuli were in place. For all groups, alternative lever presses were extinguished. The Reinstatement + Renewal group received a response-independent delivery of a food pellet at the beginning of the first session while the cues simultaneously occurred, thereafter they received cues for the target lever on a VI 20 s schedule, and Context A was reintroduced. The Reinstatement + Resurgence group received a response-independent delivery of a food pellet and simultaneous cue at the beginning of the first session, thereafter cues were delivered on a VI 20 s schedule, and the alternative lever was placed on extinction. Context A was reintroduced, and the alternative lever was placed on extinction for the Renewal + Resurgence group. The Reinstatement + Renewal + Resurgence group received a response-independent delivery of a food pellet and simultaneous cue at the beginning of the first session, thereafter cues were delivered on a VI 20 s schedule, the alternative lever was placed on extinction and Context A was reintroduced.

Data Analysis

There are several ways to evaluate relapse magnitude, each associated with strengths and weaknesses (for discussion see, Caçado et al., 2016; Lattal et al., 2017). Increases in rates of the target response between Extinction and Relapse Testing could be considered the most clinically

relevant because rate of an individual's behavior is typically tracked in clinical settings to ensure that the behavior reduction plan is working. However, this analysis may mask important differences in responding during extinction. Proportion of baseline (i.e., responding in Extinction and Relapse Testing divided by the mean terminal target response rate of an individual in Baseline) accounts for differences between response rates across subjects, and normalizing response rates allows for between-experiment comparisons. Proportion of baseline is commonly used in resurgence research because of this advantage (Berry et al., 2014; Mitteer et al., 2021; Pritchard et al., 2014) but proportional transformations can mask important differences in responding that may be relevant for practitioners (i.e., it de-emphasizes the differences in raw count or rate). For example, because the proportions are calculated based on the mean of baseline, outliers (i.e., rats with extremely high or low responding) may influence the level of the mean and mask an accurate portrayal of the data (e.g., Valbuena et al., 2017). Change score (i.e., the difference between Extinction and Relapse Testing target response rates) accounts for differences in extinction. However, it can be affected by the overall rate (e.g., the difference between one and ten is much larger than the difference between zero and one despite the same proportional increase). To offer a complete analysis of relapse effects, increases in raw target response rate between Extinction and Baseline, proportion of baseline, and change scores were used to analyze the current data. Data were statistically analyzed using ANOVAs deemed significant at an α level of .05 as described below.

Results

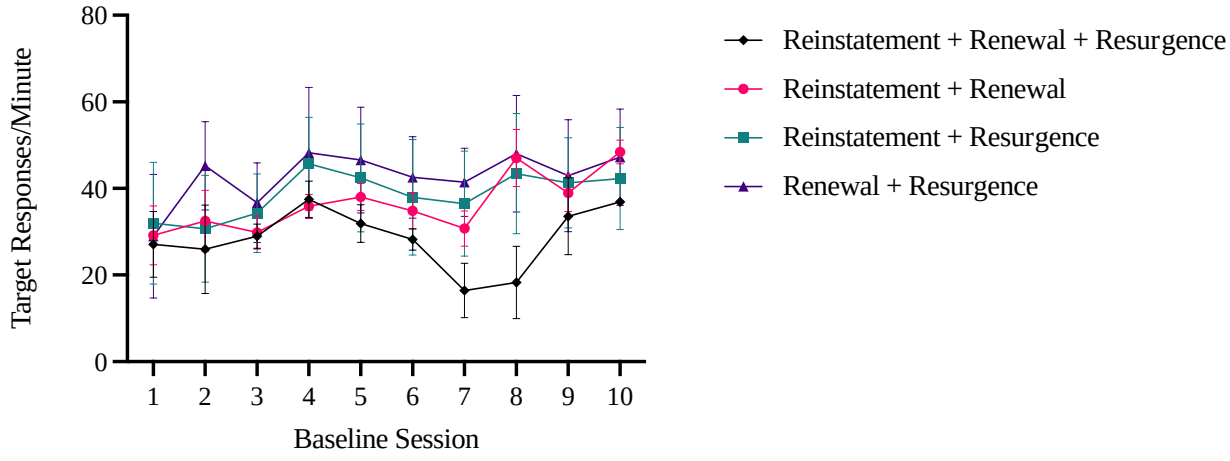
Baseline

Figure 1 shows target response rates for all rats across Baseline sessions. Target response rates increased for all groups similarly across Baseline sessions as confirmed by a 4 x 10 (Group

x Session) mixed-model ANOVA of target response rate, which revealed a significant main effect of session (F [9, 99] = 4.59, p < .001), but no significant effect of group (p = .75) and no significant group x session interaction (p = .46). The Reinstatement + Renewal + Resurgence group showed a slight decrease in responding in Baseline sessions seven and eight, but post hoc analysis using Tukey's HSD revealed no significant differences between groups in these sessions (ps >.30). By the end of Baseline, all groups response rates were similar (see Figure 1). All groups had low and similar levels of alternative responding during this phase (data not shown). Reinforcer rates increased across baseline but remained similar across groups. This finding was confirmed by a 4 x 10 (Group x Session) mixed-model ANOVA of reinforcer rates, which revealed a significant main effect of session (F [9, 99] = 3.08, p = .003), but no significant effect of group (p = .32) and no significant Group x Session interaction (p = .23). Table 2 displays a summary of reinforcer rates for each group across conditions.

Figure 1

Target Response Rates During Baseline



Note. Error bars indicate the standard errors of the mean.

Table 2

Reinforcer Rates Across Conditions

Group	Baseline	Extinction	Relapse Testing
Reinstatement + Renewal	2.76 (.05)	-	-
Reinstatement + Resurgence	2.66 (.07)	2.71 (.05)	-
Renewal + Resurgence	2.62 (.12)	2.60 (.13)	-
Reinstatement + Renewal + Resurgence	2.24 (.25)	2.17 (.53)	-

Note: The table reports both the mean (i.e., values to the left of the parentheses) and standard error of the mean (i.e., the values in parentheses).

Extinction

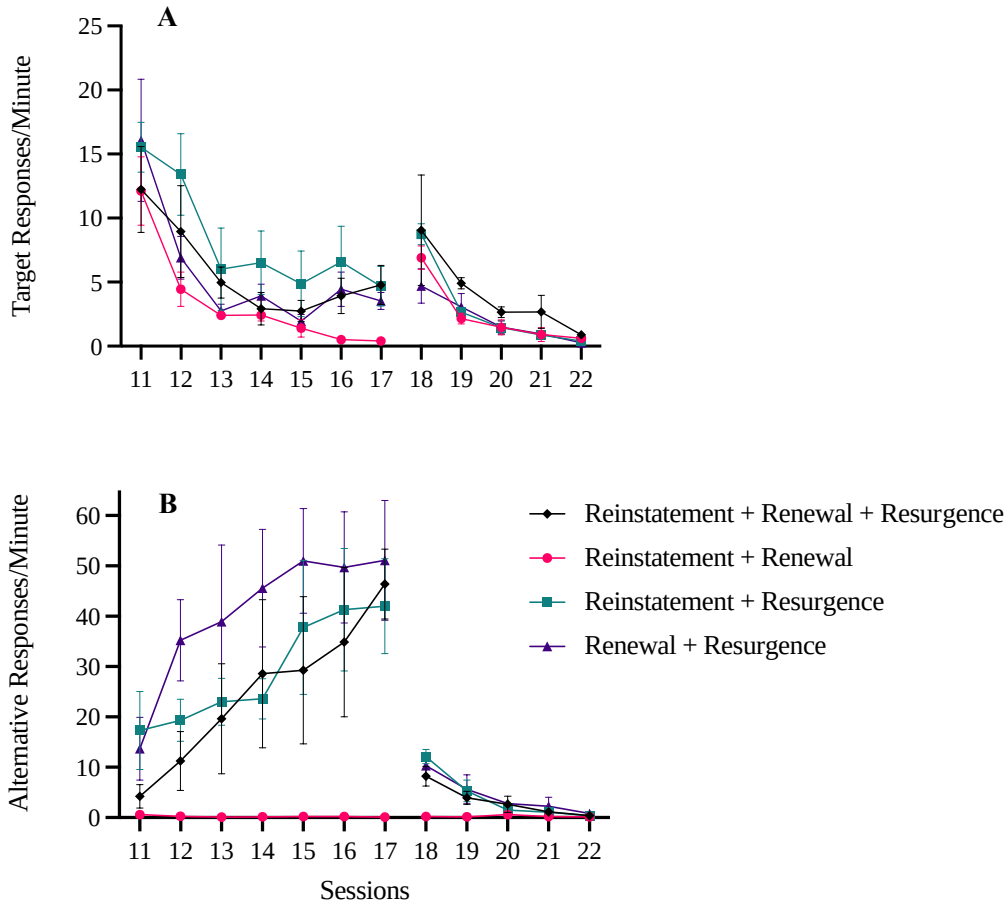
Figure 2A shows the target response rates of all groups across Extinction and Relapse Testing. Target response rates decreased for all groups similarly across Extinction, as confirmed by a 4 x 7 (Group x Session) mixed-model ANOVA of target response rate, which revealed a significant main effect of session (F[6, 66] = 24.08, $p < .001$), but no significant effect of group ($p = .15$) and no significant Group x Session interaction ($p = .95$).

Figure 2B shows the alternative response rates of all groups across Extinction and Relapse Testing. All groups except the Reinstatement + Renewal group had similar rates of alternative responding that increased across Extinction sessions. A 4 x 7 (Group x Session) mixed-model ANOVA of alternative response rates in Extinction revealed a significant main effect of session (F [6, 66] = 11.05, $p < .001$), supporting the increase in alternative responding across Extinction. A significant main effect of group (F [1,11] = 6.26, $p = .01$), and a significant Group x Session interaction (F [18, 66] = 9.18, $p = .03$) supported the conclusion that the responding across sessions depended on group. To determine the source of the significant interaction, follow up mixed-model ANOVAs were conducted on alternative response rates across Extinction between each pair of groups (see Craig et al., 2017). The interaction term remained significant only when comparing the Reinstatement + Renewal group to the other

groups (*p*s < .01). This is unsurprising, as the Reinstatement + Renewal group did not receive reinforcement for alternative responding during this phase. A 4 x 7 (Group x Session) mixed-model ANOVA of reinforcer rates in Extinction revealed a significant main effect of session (F [6, 66] = 10.43, $p < .001$), a significant main effect of group (F [1,11] = 21.58, $p < .001$), and a significant session x group interaction (F [18, 66] = 2.07, $p = .02$). To determine the source of the significant interaction, follow up mixed-model ANOVAs were conducted on reinforcer rates across Extinction between each pair of groups. The interaction term remained significant only when comparing the Reinstatement + Renewal group to the other groups (*p*s < .01). Thus, reinforcer rates increased to a similar rate across Extinction for all groups except Reinstatement + Renewal, for which reinforcement rates were zero throughout Extinction.

Figure 2

Target and Alternative Response Rates Across Extinction and Relapse Testing Sessions



Note. Error bars indicate the standard error of the mean.

Relapse Testing

Figure 2A shows that relapse of target responding occurred in all groups (i.e., there was an initial increase in target responding during relapse testing compared to the end of Extinction). Across Relapse Testing sessions, target responding decreased for all groups, but did not differ between groups. A 4 x 5 (Group x Session) mixed-model ANOVA on target response rates across Relapse Testing revealed a significant main effect of session (F [4, 44] = 39.58, p < .001),

but no significant effect of group (p = .22) and no significant group x session interaction (p = .44), confirming the results of visual analysis.

Figure 2B shows that there was a decrease in alternative response rates (compared to response rates in Extinction) during Relapse Testing. A 4 x 5 (Group x Session) mixed-model ANOVA on alternative response rates across Relapse Testing revealed a significant group x session interaction (F [18,66] = 1.89, p = .03) and significant main effects of session (F [4, 44] = 73.93, p < .001), and group (F [3,11] = 6.26, p = .01). To determine the source of the significant interaction, follow up mixed-model ANOVAs were conducted on alternative response rates across Relapse Testing between each pair of groups. The interaction term remained significant only when comparing the Reinstatement + Renewal group to the other groups (ps < .001), suggesting the significant interaction term arose from the decrease in all other groups compared to stable, low-level responding in the Reinstatement + Renewal group.

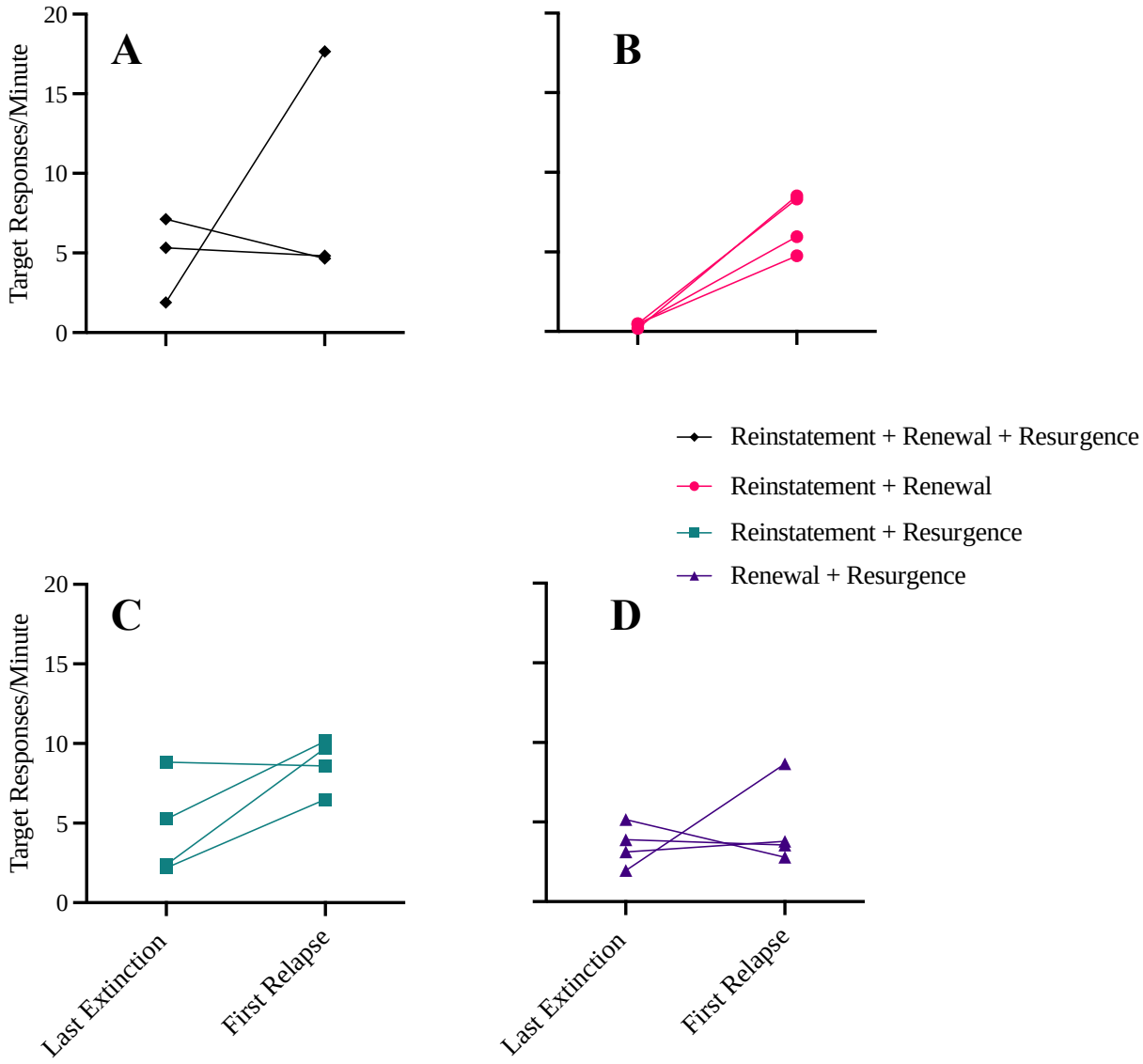
Figure 3 shows the last day of Extinction and first day of Relapse Testing for individual rats within each group. Relapse effects were confirmed by a 4 x 2 (Group by Phase [last Extinction session vs. first Relapse Testing session]) mixed-model ANOVA of target response rates, which revealed a significant main effect of phase (F [1, 11] = 9.06, p = .01) and no significant group x phase interaction (p = .56). There was a significant main effect of group (F [3, 11] = 4.22, p = .03). Visual analysis suggests the source of this group difference is lower responding in the Reinstatement + Renewal group compared to all other groups. A follow up one-way ANOVA comparing target response rates between groups on the last session of Extinction confirmed a significant effect of group (F [3,14] = 3.61, p = .05), while groups did not differ on the first session of Relapse Testing (p = .39).

Rates of stimulus deliveries decreased and were similar across groups with a reinstatement component during Relapse Testing (i.e., Reinstatement + Renewal, Reinstatement + Resurgence, & Reinstatement + Renewal + Resurgence groups; data not shown). This finding was confirmed by a 3 x 5 (Group x Session) mixed-model ANOVA on stimulus delivery rates across Relapse Testing, which revealed a significant main effect of session (F [4, 32] = 62.32, p < .001), but no significant main effect of group (p = .48), and no significant session x group interaction (p = .19).

Additional analyses using different methods to assess relapse were also conducted. Figure 4 shows change scores for all rats in each group (i.e., target response rate during the first session of Relapse Testing minus target response rate during the last session of Extinction). A one-way ANOVA of change scores revealed no significant effect of group (p = .56), suggesting relapse effects were similar between groups. Figure 5 shows the mean proportion of baseline responding for target responses for each group on the last session of Extinction and the first session of Relapse Testing. All four groups experienced some degree of relapse of target responding (i.e., showed more target responding on the first day of Relapse Testing compared to the last day of Extinction). A 4 x 2 (Group by Phase [last Extinction session vs first Relapse Testing session]) mixed-model ANOVA of proportion of baseline target response rates revealed a significant main effect of phase (F [1, 11] = 26.61, p < .001), but no significant Group x Phase interaction (p = .14) and no main effect of group (p = .57), confirming that relapse occurred and was similar for all groups.

Figure 3

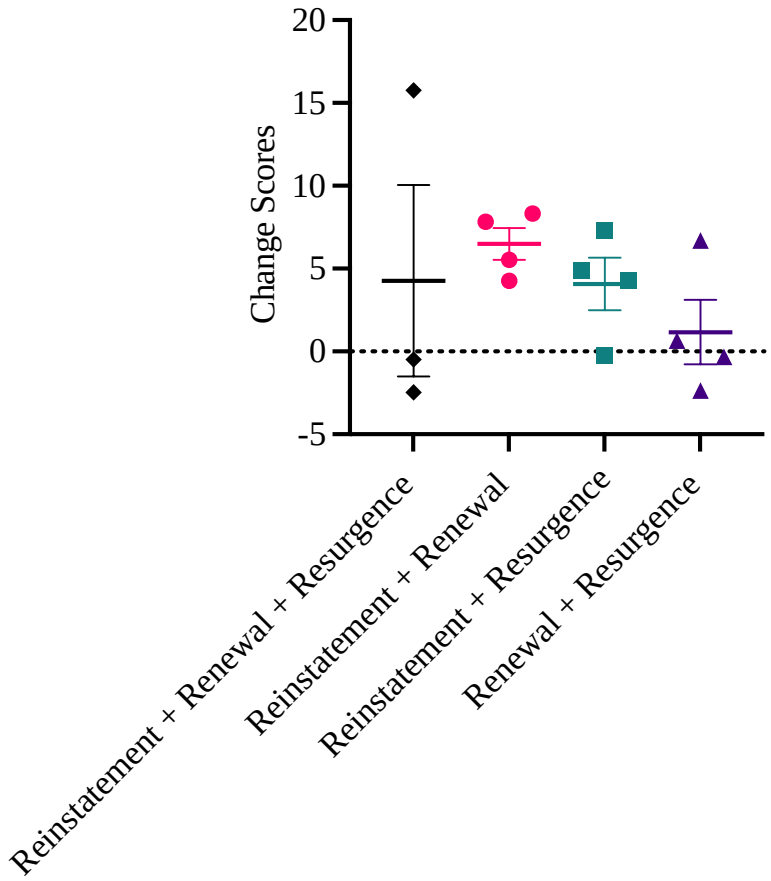
Target Response Rates on the Last Day of Extinction and First Day of Relapse Testing



Note: Panels show individual subject data from the Reinstatement + Renewal + Resurgence (A), Reinstatement + Renewal (B), Reinstatement + Resurgence (C), and Renewal + Resurgence (D) groups.

Figure 4

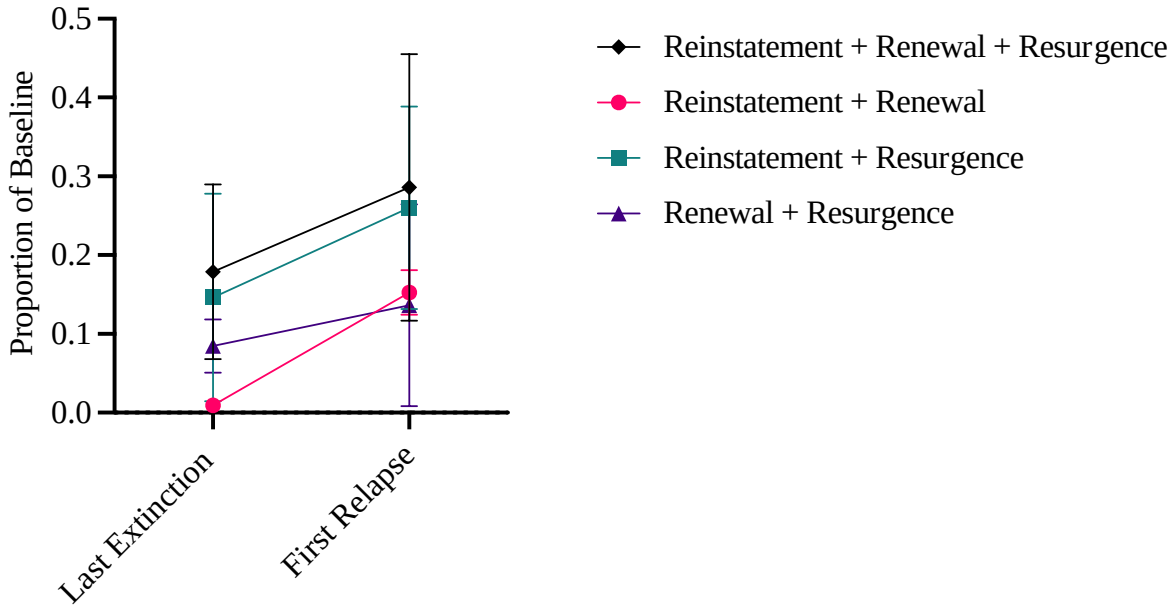
Change Scores of the Target Response Rates



Note: Change score = target response rate in the first session of Relapse Testing minus target response rate the last session of Extinction. Symbols represent individual subject data, bars represent group mean, and error bars indicate the standard error of the mean.

Figure 5

Proportion of Baseline for the Last Day of Extinction and First Day of Relapse



Note. Error bars indicate the standard error of the mean.

Discussion

One goal of ABA treatments is to reduce undesirable behavior. Multiple types of relapse are not only a likely occurrence when implementing behavior reduction plans but are also a danger to the generalization and long-term maintenance of treatments to reduce undesirable behavior. Many of the current applied relapse mitigation strategies for individual relapse types were initially developed in basic or translational studies to avoid increases in socially significant behavior and increase experimental control (e.g., Bernal-Gamboa et al., 2017a). However, existing translational models are limited to pairwise combinations of common relapse types. Therefore, the present manuscript presents a translational model for evaluating relapse induced by combinations of events using four groups of rats exposed to different combinations of events

known to induce relapse, better simulating the relapse effects that practitioners may face (i.e., multiple relapse types in combination). This study also sought to compare magnitudes of relapse across various combinations of relapse inducing events. The present data provide preliminary evidence that the magnitude of relapse was similar across groups. This could imply that any combination of relapse types will generate similar relapse effects and indicates a need for mitigation strategies that work for all types of relapse and their combinations. This may be relevant for practitioners and those in applied research because the lack of difference in relapse magnitude in the present study suggests that no particular combination is more problematic than another. Thus, it would be equally important to protect against all forms of relapse combinations. As discussed above, simultaneous implementation of several relapse mitigation strategies can be time consuming, preventing accomplishment of other goals in treatment (e.g., acquisition and maintenance of other behavior). Thus, the present study adds to prior calls for mitigation strategies that effectively reduce all forms of relapse and their combinations (e.g., Falligant et al., 2022; Kimball et al., 2023).

The similar magnitude of the relapse effects (shown in the present data) induced by different combinations of events also suggests the need for additional mitigation strategies for some forms of relapse in isolation, at least until a universally effective relapse mitigation strategy is developed. While a full description of available relapse mitigation strategies is beyond the scope of this manuscript, Kimball et al. (2023) provide a review of potential relapse mitigation strategies ranging from basic and translational procedures to human applications. Several well-documented mitigation strategies exist for resurgence and renewal. Reinstatement and its mitigation have received far less attention in the literature than resurgence and renewal (see for discussion, Kranak et al., 2022). However, the present results suggest that reinstatement effects

may be equally important for relapse following clinical treatment of problem behaviors. One notable exception to the dearth of research on reinstatement is in the substance abuse literature, where reinstatement has long been the common relapse effect examined (for reviews see, Farrell et al., 2018; Nall et al., 2021). Future work could benefit from evaluating whether reinstatement mitigation procedures developed in the substance abuse literature are effective for non-drug motivated behaviors. The present study adds to a small but recently increasing literature base on reinstatement of non-drug motivated behavior, particularly as it relates to behavior analytic treatment (e.g., Kimball et al.; 2023; Kranak & Falligant, 2023; Kranak et al., 2022). Together, the similar effects between relapse-type combinations shown here, the likelihood of reinstatement in clinical behavior reduction plans, and the relative lack of research on mitigating reinstatement suggest a need for future research into mitigation techniques for reinstatement.

An interesting finding from the present results is that all rats in the Reinstatement + Renewal group showed a decrease to near zero target responses at the end of Extinction, as well a visual trend toward having the largest relapse effect (though this difference was not statistically significant; see Figure 2A and Figure 3). Many prior studies have shown that alternative reinforcement availability decreases the rate of target responding relative to no alternative reinforcer availability (e.g., Carr & Durand, 1985; Leitenberg et al., 1975; Thompson et al. 1998). However, our results showed that the group without alternative reinforcement availability had lower target response rates during Extinction than groups with alternative reinforcement. Though this effect is less common, some other studies have demonstrated a similarly increased persistence of target behavior when alternative reinforcement is available compared to a control group that did not receive alternative reinforcement (e.g., Sweeney & Shahan, 2013, Winterbauer & Bouton, 2012). The reasons that alternative reinforcement may increase persistence of target

behavior are not clear at present. Regardless of the reasons, persistence of problem behavior during clinical treatment would be problematic. In addition to higher rates of undesirable behavior, behavior occurring more often is more susceptible to accidental reinforcement (i.e., reinstatement, as discussed above). For these reasons, future research should explicitly explore potential factors that determine when alternative reinforcement will increase or decrease persistence of target behavior.

Theories of relapse may provide one potential explanation for increased persistence of target behavior when alternative behavior is reinforced. Resurgence as Choice in Context (RaC2; Shahan et al., 2020) is a quantitative theory of resurgence with growing empirical support. Briefly, RaC2 asserts that resurgence is a product of the same variables that govern choice (i.e., RaC2 is based on the concatenated matching law; Baum & Rachlin, 1969). Shahan et al. (2020) suggested extensions of RaC2 to account for reinstatement and renewal. Podlesnik et al. (2022) further extended RaC2 by adding a parameter for reinforcer misallocation (mRaC2). Importantly, mRaC2 suggests that organisms are not perfect at detecting the source of reinforcers. Therefore, alternative reinforcers may be misallocated toward the target response. Relevant to the present study, misallocation of alternative reinforcement to the target response may explain the relatively more persistent target responding in groups other than the Reinstatement + Renewal group. Future research should further explore what factors influence reinforcer misallocation to determine how best to prevent unintentional increases in target response persistence.

To offer a complete analysis of relapse effects a variety of methods to analyze relapse were used in the current study. Changes in raw target response rate between Extinction and Baseline, proportion of baseline, and change scores all agreed that relapse occurred and was similar between groups. The analyses all showed similar relapse effects, but only the raw rate

analysis captured the difference in the Reinstatement + Renewal group during extinction, where others did not (i.e., there was no main effect of group in proportion of baseline, and no way to directly assess this with change score). Visual analysis suggested prevalence of relapse (i.e., number of rats showing an increase between extinction and relapse testing) might present a useful additional analysis. Prevalence reveals the *consistency* of the relapse effect, which is higher in the Reinstatement + Renewal group than in others. That is, 1 of 3 rats in the Reinstatement + Renewal + Resurgence group, 4 of 4 rats in the Reinstatement + Renewal group, 3 of 4 in the Reinstatement + Resurgence group, and 2 of 4 rats in the Renewal + Resurgence group showed relapse effects (see Figure 3). Each of these analytic techniques has strengths and weaknesses (see for discussion, Cançado et al., 2016; Lattal et al., 2017). Evaluating relapse with each of these standard analytic techniques allows for a more thorough analysis of relapse effects, and prevalence analyses may contribute another useful tool for future relapse studies.

There are some limitations to the present study. First, there was considerable variability in relapse effects within groups (see Figures 3 & 4). That is, only Reinstatement + Renewal produced a consistent relapse (i.e., each of the four subjects in this group showed increases in target responding between Extinction and Relapse Testing). As discussed above, responding was lower during Extinction for this group. Thus, more prominent extinction effects in the Reinstatement + Renewal group may have influenced subsequent relapse effects. Relapse was restricted to the same number of sessions across groups to control for treatment exposure in the present study. However, future studies could control for this difference in target response in extinction by evaluating relapse induced by combinations of relapse-inducing events following an extinction criteria (i.e., a minimum of two sessions with response rates at 0.5 responses per minute or lower). Similarly, larger N studies may provide additional insight into the consistency

of relapse effects induced by combinations of relapse-inducing events. That is, adding additional individuals to each group could reveal whether the inconsistency within groups seen here is a product of the contingencies or between subjects variability. Finally, the findings of this study are consistent with prior work showing that pairwise combinations of relapse-inducing events also produce relapse effects (e.g., Bouton & Trask, 2016; Kincaid et al., 2015; Liggett et al., 2018; Sweeney & Shahan, 2015; Wathen & Podlesnik, 2018). However, these prior studies have compared relapse induced by combinations of events with relapse induced by individual events to determine relative magnitudes of resulting relapse effects. Future work that directly compares relative magnitudes of individual relapse types and their combinations may be helpful for furthering understanding of the relative magnitude of relapse induced in a variety of ways relevant to clinical behavior reduction plans.

The present study evaluated three types of relapse that are likely to occur in the clinic, but other types exist. For example, spontaneous recovery can occur when a previously extinguished response reoccurs following the passage of time since extinction (Cooper et al., 2020; Rescorla, 2004). This could occur in clinical settings upon returning to the clinic (e.g., sessions resumed) following a break in treatment of problem behavior (e.g., a weekend break between sessions). This differs from renewal in that spontaneous recovery is defined by the passage of time rather than the difference in contextual stimuli. Another type of relapse is rapid reacquisition. Similar to reinstatement, rapid reacquisition is when a previously extinguished response is acquired more quickly when reinforcement is re-introduced (Bouton et al., 2004). An example is when a behavior returns rapidly when it is reinforced using the same contingencies after its extinction (Wathen & Podlesnik, 2018). Modifications can be made to the model developed here to simulate these other types of relapse. To simulate spontaneous recovery, a temporal gap between

Extinction and Relapse phases could be added. To simulate rapid reacquisition, the same reinforcement contingency from Baseline would be given after Extinction in Relapse. These modifications might assist in the development of novel mitigation strategies that incorporate these other types of relapse for which there are relatively few existing mitigation strategies (for discussion see, Wathen & Podlesnik, 2018).

Conclusion

The present study presents a translational model for evaluating relapse induced by combinations of events to better simulate the effects that practitioners may face (i.e., multiple relapse types in combination), and to compare the relative magnitude of relapse between different combinations of relapse types. The present data provide preliminary evidence that relapse may be similar across combinations of environmental changes that induce reinstatement, resurgence, and renewal. This supports recent calls by others to develop relapse mitigation techniques that are effective for common relapse types and their combinations. The model developed here could be a useful tool to assess the efficacy of such mitigation techniques and may be a first step in the development of a universally effective relapse mitigation technique.

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Appendix A

Approval Letter

Institutional Animal Care and Use Committee (IACUC)
700 Pelham Road North
Jacksonville, AL 36265-1602

TO: Rusty Nall, Ph.D.
FROM: Grover Brown, Ph.D.
DATE: October 25th, 2023
SUBJECT: Approval of Animal Use Protocol

Your animal use protocol submission entitled, "Comparing Relapse Magnitude Across Reinstatement, Renewal, Resurgence, and their Combinations," has been reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The IACUC approval number for this protocol
is 001-10-25-23. You may now post this protocol number in your lab.

Date of Approval: 10/25/2023
Date of Expiration: 10/25/2026

Please note that any protocol changes, increases in animal numbers, or addition/removal of personnel must receive approval by the IACUC.

This approval is valid for a three-year period. If work continues beyond the expiration date, a new protocol will need to be submitted and approved by the IACUC prior to 10/25/2026. Additionally, federal regulations and campus policy require semi-annual administrative review of protocols. You will receive notification from the IACUC prior to the deadlines for these reviews as well as for the protocol expiration.

If you have any questions, please do not hesitate to contact the IACUC staff.

Sincerely,

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