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Foot shock facilitates reward seeking in an experience-dependent manner

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ABSTRACT

Animals organize reward seeking around aversive events. An abundance of research shows that foot shock, as well as a shock-associated cue, can elicit freezing and suppress reward seeking. Yet, there is evidence that experience can flip the effect of foot shock to facilitate reward seeking. Here we examined cue suppression, foot shock suppression and foot shock facilitation of reward seeking in a single behavioural setting. Male Long Evans rats received fear discrimination consisting of danger, uncertainty, and safety cues. Discrimination took place over a baseline of rewarded nose poking. With limited experience (1–2 sessions), all cues and foot shock suppressed reward seeking. With continued experience (10–16 sessions), suppression became specific to shock-associated cues, foot shock briefly suppressed, then facilitated reward seeking. Our results provide a means of assessing positive properties of foot shock, and may provide insight into maladaptive behaviour around aversive events.

1. Introduction

Animals must navigate a perilous world to secure essential rewards. Studies of associative learning and defensive behaviour reveal that animals are adept at organizing reward seeking around aversive events. Even more, this organization changes as a function of experience. Picture a mildly hungry rat pressing a lever for food. Presenting an innocuous cue will produce little change in the rat's reward seeking behaviour. A foundational report by Estes and Skinner (1941) demonstrated that a cue will acquire aversive properties when paired with foot shock [1]. A shock-associated cue will sharply reduce reward seeking. Historically termed a conditioned emotional response [2–5], now commonly termed conditioned suppression, the ability of a shock-associated cue to suppress reward seeking has been observed in many settings and laboratories [6–16].

Like their associated cues, aversive events alter behaviour. Picture a rat exploring a novel environment when foot shock is unexpectedly delivered. Foot shock delivery will elicit a brief, undirected activity burst, followed by freezing [17–20]. While theoretical accounts vary [21–23], the behavioural phenomenon of post shock freezing is widely observed [24–28]. Foot shock can also suppress reward seeking [29], and the organization of reward seeking around foot shock changes with experience [30]. In their original demonstration, Estes and Skinner noted a compensatory increase in reward seeking following shock termination. LaBarbera and Caul (1976) later demonstrated that foot shock can facilitate reward seeking above baseline levels, and the magnitude of facilitation increases with foot shock experience [19]. These findings indicate that reward seeking around an aversive event may change dramatically with experience.

Studies of shock-associated cue suppression of reward seeking, post shock freezing, and post shock facilitation of reward seeking are typically carried out in isolation. These studies have utilized different dependent measures of behaviour: ratios derived from rates of reward seeking, freezing, and instrumental response rates. By necessity, these studies differed in basic experimental details: foot shock intensity, foot shock duration, cue type, cue length, etc. Our laboratory has developed a discriminative, conditioned suppression procedure in which distinct auditory cues predict unique foot shock probabilities: danger (p=1.00), uncertainty (p=0.25) and safety (p=0.00). Cues are presented over a baseline of rewarded nose poking, and poke-reward contingencies are independent from cue-shock contingencies. Using this procedure, we have observed a consistent, experience-dependent pattern of discrimination. Initial suppression of nose poking to all cues gives way to graded levels of nose poking that generally reflects shock probability: danger < uncertainty < safety [31–36]. The goal of this study was to examine cue suppression, post shock suppression and post shock facilitation of

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reward seeking in a single behavioural setting. By examining nose poke rate in discrete time periods within trials and across discrimination, we were able to reveal how experience shapes reward seeking around foot shock and shock-associated cues.

2. Materials and methods

2.1. Subjects

Subjects were 123 male Long Evans rats pooled from 9 different studies (n = 15, 17, 13, 11, 21, 7, 21, 8, 10). 110 were obtained from Charles River (26 shipped ~21 day olds, 84 ~50 days old) and 13 were born in the Boston College Animal Care Facility. Those born in the Boston College Animal Care Facility were housed with mothers until postnatal day 21 when they were weaned and single housed. All rats were maintained on a 12 -h light-dark cycle (lights on 0600–1800) and were aged approximately 74–84 days at the start of fear discrimination, throughout which they were maintained at 85% of their free-feeding body weight and received water ad libitum. Eighty-four subjects received sham lesions prior to fear discrimination in the following brain regions: lateral habenula (n=17), orbitofrontal cortex (n=21) [33], ventral pallidum (n=7), nucleus accumbens core (n=21) [36], retrorubral field (n=14), and dorsal raphe (n=4). Twenty-four of the rats not given sham lesions received additional handling in adolescence. The remaining fifteen rats had access to a second water bottle during adolescence. ANOVA revealed that baseline and cue nose poke rates did not differ between treatments (sham lesion vs. adolescent handling vs. adolescent access to a second water bottle). All protocols were approved by the Boston College Animal Care and Use Committee, and all experiments were carried out in accordance with the NIH guidelines regarding the care and use of rats for experimental procedures.

2.2. Apparatus

The apparatus for fear discrimination consisted of eighteen individual sound-attenuated enclosures that each housed a behaviour chamber with aluminum front and back walls, clear acrylic sides/top, and a metal grid floor. Each grid floor bar was electrically connected to an aversive shock generator (Med Associates, St. Albans, VT). A single food cup and central nose poke opening equipped with infrared photocells were present on one wall. Auditory stimuli were presented through two speakers mounted on the ceiling of each enclosure.

2.3. Nose poke acquisition

All rats were first provided pellets (Bio-Serv, Flemington, NJ) for two days in the home cage. Rats were then shaped to nose poke for these pellets in the experimental chamber. During the first session, the port was removed, and rats were issued one pellet every 60s for 30 min. In the next session, the port was reinserted, and poking was reinforced on a fixed ratio 1 schedule in which one nose poke yielded one pellet until they reached ~50 nose pokes. Nose poking was then reinforced on a variable interval 30-second (VI-30) schedule for one session, then a VI-60 schedule for the next four sessions. The VI-60 reinforcement schedule was utilized during subsequent fear discrimination and was completely independent of auditory cue and foot shock presentation.

2.4. Pre-exposure

Each rat was pre-exposed to the three auditory cues in two sessions. Auditory cues were 10s in duration and consisted of repeating motifs of a broadband click, phaser, or trumpet. Previous studies have found these stimuli to be equally salient, yet discriminable [31–33]. Stimuli available here: http://mcdannaldlab.org/resources/ardbark. The 42-min pre-exposure sessions consisted of at least 5 min of initial habituation, four presentations of each cue (12 total presentations) with a mean inter-trial interval (ITI) of 3 min. The order of trial type presentation was randomly determined by the behavioural program and differed for each rat during each session.

2.5. Fear discrimination

For the next sixteen sessions, all rats underwent Pavlovian fear discrimination. Each 54-min session began with a five minute warm-up period during which time no cues or foot shock were presented. During fear discrimination, each auditory cue predicted a unique foot shock (0.5mA, 0.5s) probability: danger, p=1.00; uncertainty, p=0.25; and safety, p=0.00. For 21 of the rats the foot shock was administered 1s following termination of the cue on danger and uncertainty shock trials. An uncertainty cue with 25% foot shock probability is used because initial work found that an uncertainty cue with 50% foot shock probability will produce suppression of nose poking that is comparable to the danger cue [39]. For the remaining 102 rats, foot shock was administered 2s after cue termination on danger and uncertainty shock trials. A single session consisted of 4 danger, 2 uncertainty-shock, 6 uncertainty-no shock, and 4 safety trials with a mean inter-trial interval of 3 min. Trial order was randomly determined by the behavioural program and differed for each rat, every session. The physical identities of the auditory cues were counterbalanced across individuals.

2.6. Analysis

Timestamps for nose poke, cue onset, and shock onset were collected with Med Associates software. Nose poke rates (pokes/min) were calculated in 1-s bins aligned to cue onset and shock offset. One analysis focused on nose poke rates during four *a priori* periods of interest (Fig. 1A): baseline – 10s prior to cue onset, cue – 10s cue period, immediate post shock – first 2s after shock offset, and delay post shock – 4s period starting 3s after shock offset. The immediate and delay post shock periods were separately analyzed based on prior work showing that foot shock produces an immediate activity burst that gives way to freezing [17]. Another analysis focused on second by second nose poke rates around cue onset and shock offset. Differential nose poke rates between shock and no shock trial types were used to determine relative suppression/facilitation. Comparing cue and post shock nose pokes rates to baseline determined absolute suppression/facilitation. Both were examined using 95% bootstrap confidence intervals.

3. Results

Our laboratory has observed robust danger, uncertainty, and safety discrimination using suppression ratios calculated from rates of rewarded nose poking [31,32,35–37]. Classic studies examining defensive behaviour have reported robust post shock freezing [18,25,38]. To determine if cue-elicited and shock-elicited behaviours are observed in a common measure, we first analyzed nose poke rates for our four *a priori* periods of interest over the 16 discrimination sessions. ANOVA with factors of trial type (danger, uncertainty-shock, uncertainty-omission and safety) and session (1–16) were conducted on mean nose poke rates (averaging across all time bins for each period, for each subject). Baseline nose poke rates did not differ between trial types and increased over sessions (Fig. 1B), confirmed by a significant effect of session ($F_{15,1830}$ = 119.77, p= 1.65×10^{-258}, η_p^2 = 0.49, op = 1.0), no significant effect of trial type ($F_{3,366}$ = 0.80, p=0.49, η_p^2 = 0.007, op = 0.20), and no interaction between trial type and session ($F_{45,5490}$ = 1.16, p=0.21, η_p^2 = 0.009, op = 0.90). The results reduce concerns that trial type differences in nose poking during cue and post shock periods were the result of baseline differences.

Consistent with previous reports using suppression ratios, measuring nose poke rate revealed complete discrimination of danger, uncertainty and safey [31,32,39]. Nose poking was reduced to all cues between the first and second sessions, but fear discrimination emerged thereafter.

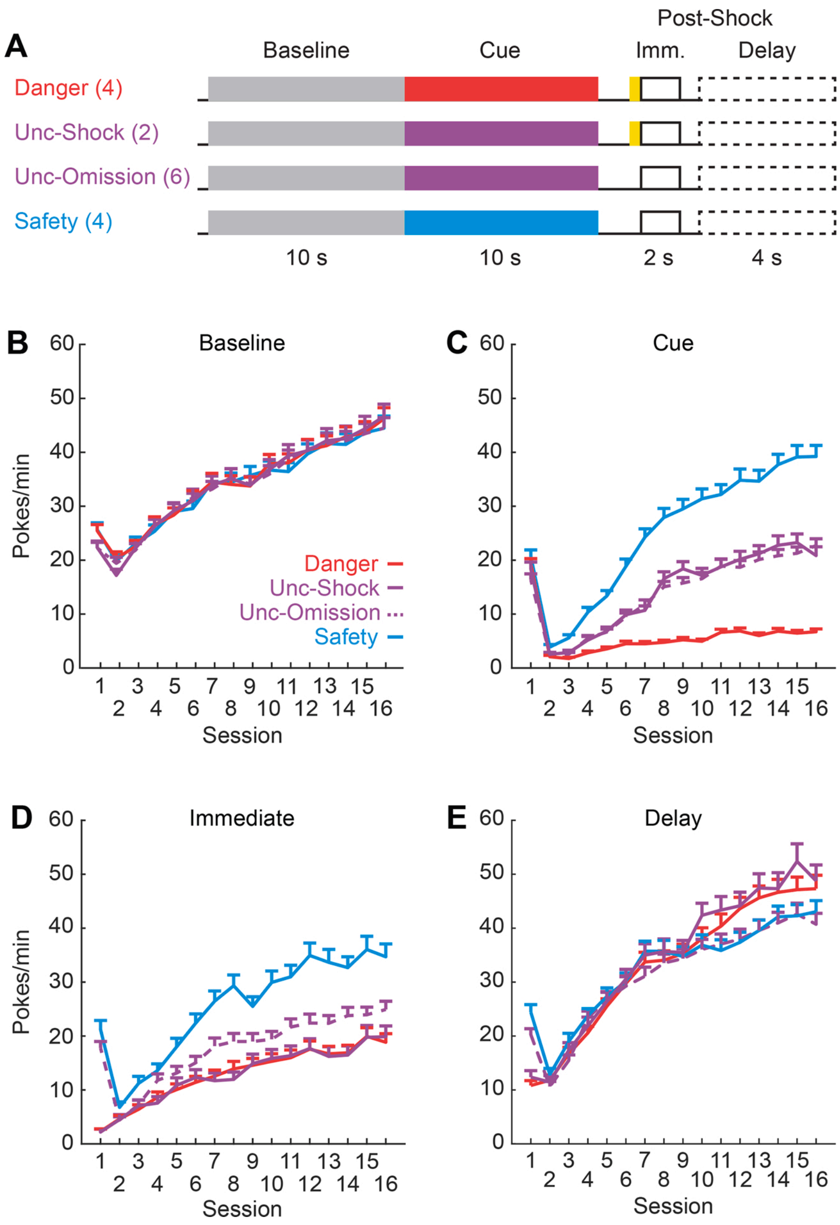

Fig. 1. Experimental outline and session by session nose poking.
Trial schematic showing the four periods of interest for danger (red), uncertainty (purple) and safety (blue) trial types (A). Mean + SEM nose poke rate in each session of fear discrimination during baseline (B), cue (C), immediate post shock (D), and delay post shock (E) periods. Gray bar, baseline; yellow bar, foot shock. Error bars show + SEM.

Nose poke rates showed the greatest increase over sessions during safety, an intermediate increase during uncertainty and the least increase during danger (Fig. 1C). This pattern was confirmed by significant effects of trial type($F_{3,366} = 234.70$, p=6.71×10^{-85}, $\eta_p^2 = 0.66$, op = 1.0), session ($F_{15,1830} = 141.16$, p=5.73×10^{-292}, $\eta_p^2 = 0.54$, op = 1.0), and importantly a significant trial type x session interaction ($F_{45,5490} = 40.08$, p=7.56×10^{-299}, $\eta_p^2 = 0.25$, op = 1.0). Paired samples t-tests ($p<0.00104$, Bonferroni corrected for 48 tests) revealed that cue nose poke rates did not differ for uncertainty-shock and uncertainty-omission in any session (all $p>0.006$). In all sessions safety nose poke rates were significantly higher than uncertainty-omission (all $p<0.00019$), and in all sessions but the first three ($p>0.009$), danger nose poke rates were significantly lower than nose poke rates during uncertainty-shock (all $p<0.00036$).

Consistent with post shock freezing reports, nose poking was reduced immediately following foot shock delivery on danger and uncertainty-shock trials during the first session. Reduced nose poking generalized to all trial types by the second session. Nose poke rates increased in subsequent sessions, with the greatest increase following safety, a lesser increase following uncertainty-omission and the least increase following foot shock trial types (danger and uncertainty-shock, Fig. 1D). This pattern was confirmed by ANOVA for nose poke rate during the immediate post shock period, which revealed significant effects of trial type ($F_{3,366} = 55.03$, p=2.21×10^{-29}, $\eta_p^2 = 0.31$, op = 1.0), session ($F_{15,1830} = 77.81$, p=1.97×10^{-183}, $\eta_p^2 = 0.39$, op = 1.0), and a significant trial type x session interaction ($F_{45,5490} = 4.12$, p=1.35 ×10^{-18}, $\eta_p^2 = 0.033$, op = 1.0).

The baseline, cue, and immediate post shock results confirm that well-known behavioural consequences of shock-associated cues and shock delivery are observed when measuring nose poke rates. A distinct pattern emerged in the post shock, delay period. Like for the immediate period, nose poking was reduced between the first and second sessions. Through session 8, there was little difference in nose poke rates between the four trial types. However, in all remaining sessions, nose poke rates *increased* following foot shock (danger and uncertainty-shock trial types) compared to trial types with no foot shock (safety and uncertainty-omission trial types). Foot shock facilitated rewarded nose poking during the delay period. Descriptions were confirmed by ANOVA which found significant effects of trial type ($F_{3,366} = 8.58$, p=0.000016, $\eta_p^2 = 0.066$, op = 0.99), session ($F_{15,1830} = 136.65$, p=3.81×10^{-285}, $\eta_p^2 =$

0.53, op = 1.0) and a significant trial type x session interaction ($F_{45,5490} = 5.62$, $p = 7.02\times10^{-30}$, $\eta_p^2 = 0.044$, op = 1.0).

3.1. *Shock facilitation of nose poking emerges over discrimination*

To directly compare nose poke rates during shock and no-shock trial types, difference scores were calculated for all 16 sessions, for each *a priori* period of interest. Mean nose poke rates during uncertainty-omission trials were subtracted from uncertainty-shock trials; and mean nose poke rates during safety trials were subtracted from danger trials. Calculating difference scores between trial types provided a *relative* measure of suppression/facilitation. This was particularly important for the post shock periods. Negative scores indicated relative suppression (reduced nose poking during trial types with shock delivery, compared to trial types with shock omission) while positive scores indicated relative facilitation (increased nose poking during trial types with shock delivery, compared to trial types with shock omission). Meaningful differences in nose poke rates between trial types were determined by constructing 95% bootstrap confidence intervals for differential nose poke rates, for each period of interest. Intervals that did not contain zero supported differential nose poke rates between trial types for that session/period. Note that a 95% bootstrap confidence interval indicates whether a population distribution is shifted from zero. A population may be positively shifted from zero, yet some individuals may show negative values.

As expected, there was little difference in baseline nose poke rates between the two uncertainty trial types, and between danger and safety trials across discrimination sessions. 95% bootstrap confidence intervals for differential nose poke rates contained zero in all but one session (Fig. 2A; session 2 uncertainty difference score did not contain zero (M = −2.26, 95% CI [−0.37, −3.91]). Also as expected, there was little difference between nose poke rates during the uncertainty trial types during the cue period (Fig. 2B). Only the 95% bootstrap confidence interval for session 9 did not contain zero (M = 2.64, 95% CI [4.58, 2.64]). Demonstrating rapid and robust acquisition of discrimination, rats showed differential nose poke rates to danger and safety in every session except for the first (95% bootstrap confidence intervals did not contain zero). The mean difference score for danger and safety increased each session, reaching a difference of -32.5 pokes/min by session 16.

Consistent with post shock freezing, first session nose poke rates were more greatly reduced following uncertainty-shock trials compared to uncertainty-omission during the immediate post shock period. Somewhat surprisingly, from session 2 onwards this difference was minimized. Differential nose poking during the immediate period hovered just below zero, with only sessions 1, 4, 7, 8, & 14 showing reduced nose poke rates on shock trials (Fig. 2C). Comparing danger and safety revealed a more consistent pattern. Nose poke rates were lower immediately following shock during danger trials, compared to the immediate period during safety trials. Apart from session 2 (M = −2.2, CI [−3.8, −0.6]), the 95% bootstrap confidence interval did not contain zero for any interval (Fig. 2C). This result should be interpreted with caution. Rats suppressed nose poking during danger cue presentation, but less so during safety cue presentation. Reduced nose poking immediately following shock presentation on danger trials may simply be a continuation of suppression already established by the cue, rather than suppression newly established by foot shock.

We were most interested in the pattern of differential reward seeking during the delay period (Fig. 2D). For both trial type comparisons, a reduction in nose poking was observed during the post shock delay period in the first session (95% bootstrap confidence intervals did not contain zero for uncertainty-shock vs. uncertainty-omission, and danger vs. safety). With the exception of the danger/safety comparison in

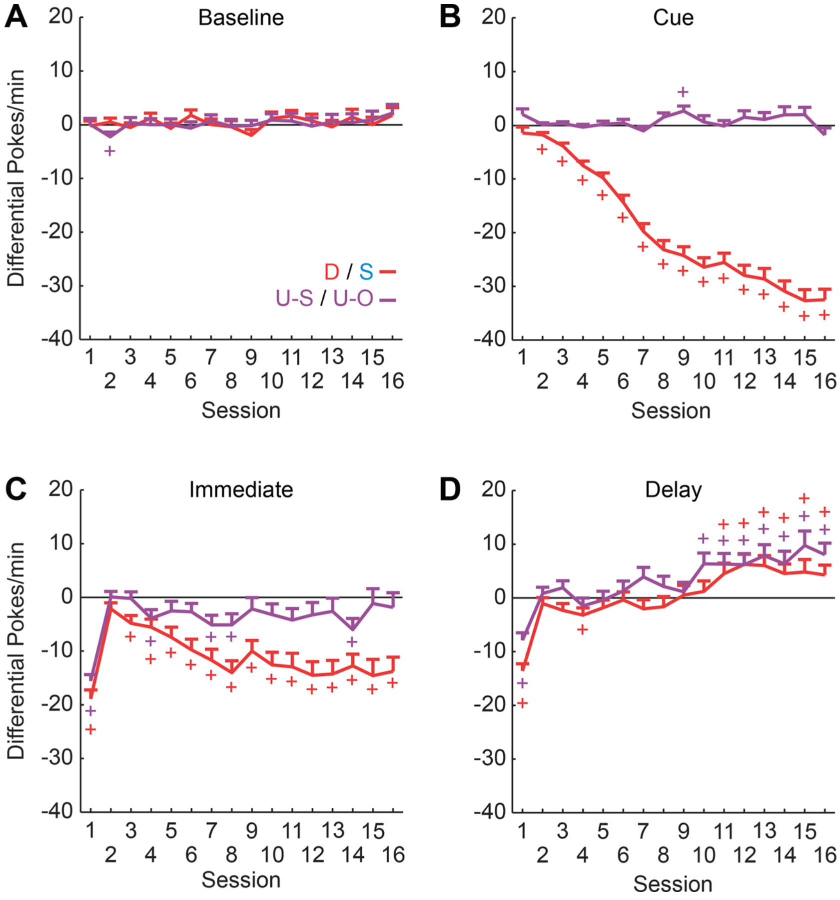

Fig. 2. Differential nose poking on shock and omission trials over sessions.

Mean + SEM differential nose poke rate across sessions of fear discrimination: uncertainty-omission trials subtracted from uncertainty-shock (purple), safety trials subtracted from danger trials (red), during baseline (A), cue (B), immediate post shock (C), and delay post shock (D) periods. $^{+}$95% bootstrap confidence interval does not contain zero.

session 4 ($M = -3.2$ [$CI = -5.7, -0.73$]), no subsequent reduction was observed. By the end of discrimination, higher nose poke rates were observed during the delay period following foot shock, relative to no-shock trials. Relative facilitation following uncertainty-shock delivery was observed during each of the final 7 sessions (10–16), and relative facilitation following danger-shock delivery was observed during each of the final 6 sessions (11–16; 95% bootstrap confidence intervals did not contain zero).

3.2. Reduction, then facilitation of nose poking following foot shock

To examine the time course of nose poking following shock delivery, we focused on nose poke rates in the final six sessions. We calculated mean nose poke rates for the final 2, 1-s baseline intervals, 10, 1-s cue intervals and 10, 1-s post shock intervals. As expected, no differences in baseline nose poking were observed between trial types (Fig. 3A). Nose poke rates were reduced for all cues in the first interval, although differential nose poking was evident (safety > uncertainty-omission = uncertainty-shock > danger). From the second interval on, the full discrimination pattern was evident (Fig. 3A). ANOVA with trial type and time (1-s interval) as factors confirmed a significant effect of trial type ($F_{3,366} = 228.87$, $p{=}1.37{\times}10^{-83}$, $\eta_p^2 = 0.65$, op = 1.0), time ($F_{9,1098} = 15.10$, $p{=}2.42{\times}10^{-23}$, $\eta_p^2 = 0.110$, op = 1.0), as well as a significant interaction between trial type and time ($F_{27,3294} = 14.23$, $p{=}7.32{\times}10^{-61}$, $\eta_p^2 = 0.10$, op = 1.0). Importantly, nose poke rates differed between danger and safety for every cue interval (95% bootstrap intervals did not contain zero), but did not differ between uncertainty-shock and uncertainty-omission for any cue interval (95% bootstrap intervals contained zero).

The pattern of reward seeking showed a dramatic but consistent change during the 10 s following shock offset (Fig. 3B). In the first 1 s interval, nose poking was most greatly reduced following uncertainty-shock and danger, somewhat less to uncertainty-omission and least to safety. This pattern eroded in the second interval, and in subsequent intervals nose poking sharply increased for uncertainty-shock and danger trials. This trend continued, with uncertainty-shock and danger nose poke rates eclipsing uncertainty-omission and safety rates, peaking ~5−6 seconds following shock offset. Nose poke rates normalized in the final ~3 s seconds. ANOVA confirmed a significant effect of trial type ($F_{3,366} = 6.92$, $p{=}0.00015$, $\eta_p^2 = 0.054$, op = 0.98), time ($F_{9,1098} = 125.05$, $p{=}1.86{\times}10^{-161}$, $\eta_p^2 = 0.51$, op = 1.0), and trial type x time interaction ($F_{27,3294} = 16.40$, $p{=}1.64{\times}10^{-71}$, $\eta_p^2 = 0.12$, op = 1.0).

3.3. Absolute foot shock suppression gives way to absolute facilitation

The strongest case for facilitation would be made if nose poking did not only increase following foot shock, but increased over baseline nose poking levels. To determine absolute changes in nose poking, we compared nose poke rates in each 1 s, post shock interval to baseline. Negative values indicated absolute suppression (nose poking below baseline levels) and positive values indicated absolute facilitation (nose poking above baseline levels). 95% bootstrap confidence intervals were constructed for each 1 s interval, for each trial type (Fig. 3B, plus marks indicate 95% bootstrap confidence intervals did not contain zero).

For all trial types, absolute suppression was observed during the first two intervals following shock offset (95% bootstrap confidence intervals did not contain zero for any trial type/interval). Afterwards, trial type-specific patterns emerge. Nose poke rates following uncertainty-shock reached baseline levels by the third interval, were increased over baseline during the next 5 intervals (seconds 4–8), then returned to baseline levels. Revealing absolute facilitation, 95% bootstrap confidence intervals did not contain zero for intervals 4–8 (Fig. 3B, solid purple). Nose poke rates following danger shock reached baseline levels by the fourth interval, and were increased over baseline during the next 6 intervals. Again revealing absolute facilitation, 95% bootstrap confidence intervals did not contain zero for intervals 5–10 (Fig. 3B, red).

To visualize the distribution of absolute suppression/facilitation across individuals, difference scores (period - baseline) were calculated

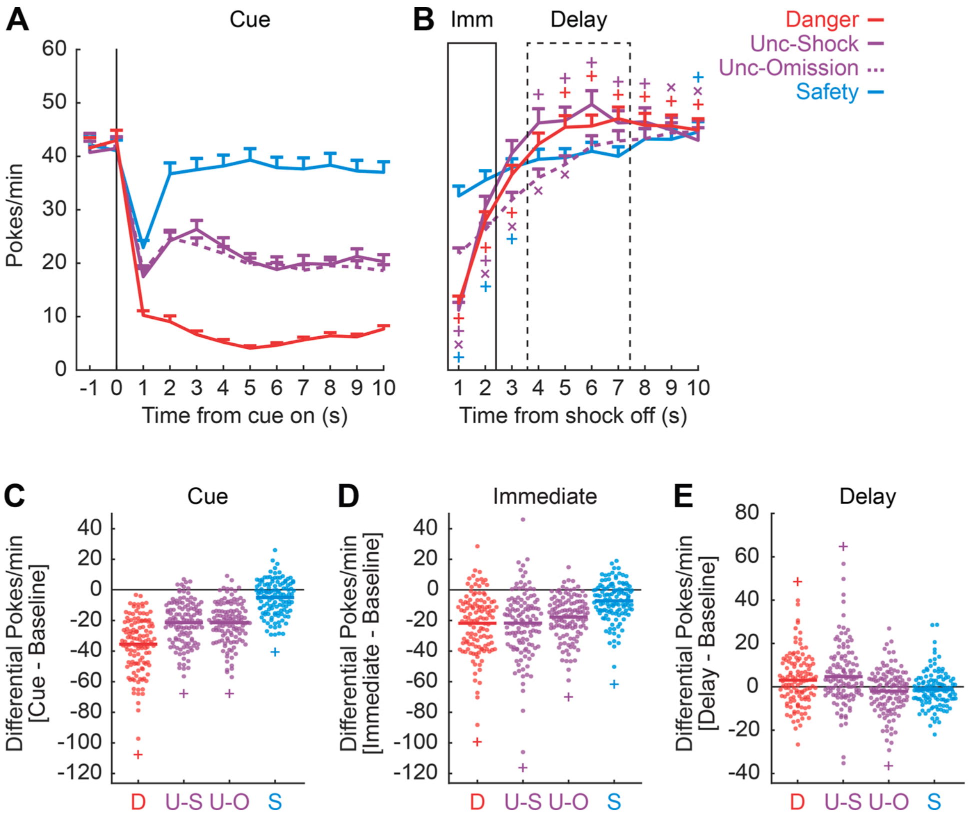

Fig. 3. Nose poking in 1 s intervals around cue and shock.
Mean + SEM nose poke rate during 1 s interval: 2 s baseline → 10 s cue (A), 10 s post shock (B). Solid box indicates immediate post shock period, dashed box indicates delay post shock period. Baseline subtracted nose poke rate for each subject shown for each trial type (D = danger, U-S = uncertainty-shock, U-O = uncertainty-omission, S = safety), during cue (C), immediate (D), and delay (E) periods. $^{+}$95% bootstrap confidence interval does not contain zero.

for each individual/trial type for each *a priori* period, and 95% bootstrap confidence intervals constructed (Fig. 3). Decreases in nose poking under baseline were observed for each trial type during the 10-s cue period (Fig. 3C). Similarly, decreases in nose poking under baseline were observed for each trial type during the immediate shock period (Fig. 3D). Revealing absolute facilitation, increases in nose poking over baseline during the delay period were observed for danger (~110% of baseline, M = 3.06, 95% CI [0.96, 4.96]) and uncertainty-shock trials (~115% of baseline, M = 4.73, 95% CI [2.03, 7.26]). Decreases in nose poke rate were observed to uncertainty-omission (~99% of baseline, M = −1.98, 95% CI [−3.64, −0.24]), while safety nose poke rates did not differ from baseline (~102% of baseline, M =−1.22, 95% CI [−2.60, 0.05]). So while individual variation was present, absolute facilitation following foot shock delivery during the delay period was readily observed at the population level.

3.4. *Relative foot shock suppression gives way to relative facilitation*

To test for relative changes in nose poking during shock and no-shock trial types, we constructed 95% bootstrap confidence intervals for differential nose poke rate for both danger/safety and uncertainty-shock/uncertainty-omission. Relative suppression to danger compared to safety was observed for every cue interval (Fig. 4A; no 95% bootstrap confidence interval contains zero). No differences in nose poke rates were observed for the uncertainty trial types. 95% bootstrap confidence intervals found equivalent nose poke rates during every interval for uncertainty-shock and uncertainty-omission trial types (Fig. 4A; every 95% bootstrap confidence interval contains zero).

95% bootstrap confidence intervals confirmed lower nose poke rates during the first post shock interval on uncertainty-shock trials compared to uncertainty-omission. Nose poke rates during uncertainty-shock trials exceeded those for uncertainty-omission trials in each of the next six intervals, as confirmed by the 95% bootstrap confidence intervals not including zero. Nose poke rates during shock and no shock trial types were equivalent during the final 3 intervals, with all confidence intervals including zero. Comparing danger and safety trials revealed a similar pattern but with fewer intervals demonstrating facilitation. This is likely because safety nose poke rates remained high throughout the post shock period. Nevertheless, reduced nose poking to danger during the first two intervals gave way to enhanced nose poking to danger during intervals 5−7. No bootstrap confidence intervals contained zero for these intervals. Nose poke rates converged in the final 3 intervals, confirmed by all 95% bootstrap confidence intervals including zero.

To visualize the distribution of relative suppression/facilitation across individuals, difference scores for each trial type comparison were calculated for each individual/period, and 95% bootstrap confidence intervals constructed (Fig. 4C–E). Danger nose poke rates were suppressed relative to safety nose poke rates during the cue period (M = −29.7, CI [−32.9, −26.4]), whereas no differences were observed for uncertainty-shock and uncertainty-omission trials (95% bootstrap confidence interval contains zero). Relative suppression was observed for both trial type comparisons during the immediate shock period (Fig. 4D). Danger nose poke rates were ~59% of safety, (M = −13.7, CI [−17.4, −9.7]) and uncertainty-shock nose poke rates were ~86 % of uncertainty-omission, (M = −3.2, CI [−6.0, −0.27]). Critically, relative facilitation was observed for both trial type comparisons during the delay period (Fig. 4E). Danger nose poke rates were ~112% of safety (M = 5.09, CI [2.6, 7.2]), and uncertainty-shock nose poke rates were ~118% of uncertainty-omission (M = 7.5, CI [5.0, 9.8]). Although individual variation was present, relative facilitation was observed across the population during the delay period.

3.5. *Foot shock facilitation of nose poking is a distinct behavioural mechanism*

We were curious if foot shock facilitation of reward seeking was related to other aspects of behaviour and fear discrimination. We first compared foot shock facilitation of reward seeking to baseline nose poke rate. For example, rats showing higher baseline poking may show stronger facilitation. Baseline nose poke rate was unrelated to the

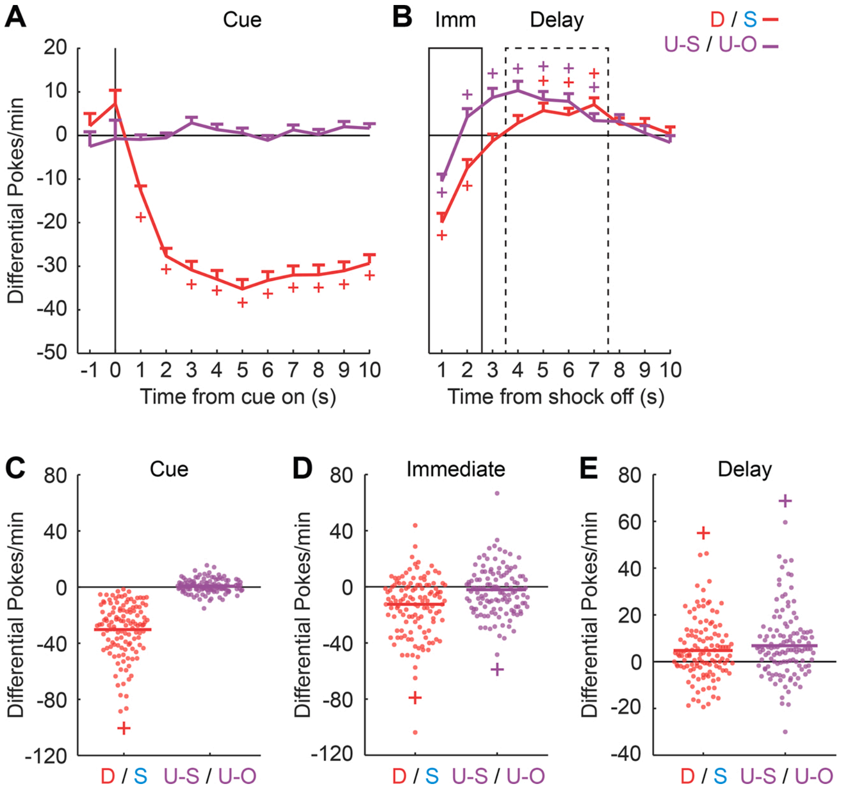

Fig. 4. Differential nose poking on shock and omission trials in 1 s intervals around cue and shock.

Mean + SEM differential nose poke rate during 1 s interval: 2 s baseline → 10 s cue (A), 10 s post shock (B). Safety subtracted from danger (D/S, red) and uncertainty-omission subtracted from uncertainty-shock (U-S/U-O, purple). Solid box indicates immediate post shock period, dashed box indicates delay post shock period. Differential nose poke rate for each subject shown for each period: cue (C), immediate post shock (D), and immediate delay (E) periods. $^{+}$95% bootstrap confidence interval does not contain zero.

magnitude of foot shock facilitation. Zero relationships with baseline were observed for uncertainty-shock ($R^2 = 1.49\times10^{-4}$, p=0.89) and danger ($R^2 = 0.001$, p=0.70). Perhaps rats showing better discrimination showed superior facilitation. Foot shock facilitation during the delay period was now compared to differential poke rates for danger and safety from the cue period (Fig. 5C, D). Zero relationships with discrimination were observed for uncertainty-shock ($R^2 = 0.01$, p=0.25) and danger ($R^2 = 0.01$, p=0.25). Finally, we compared foot shock suppression during the immediate period to foot shock facilitation during the delay period (Fig. 5E, F). For example, more strongly suppressed reward seeking during the immediate period could result in a greater 'acceleration' of reward seeking during the delay period. Again, zero relationships with suppression were observed for uncertainty-shock ($R^2 = 0.02$, p=0.12) and danger ($R^2 = 0.01$, p=0.22). The only relationship was within facilitation itself. Foot shock facilitation of reward seeking during the delay period was positively correlated for danger and uncertainty-shock trials (Fig. 5G, $R^2 = 0.35$, $p=3.67\times10^{-13}$).

4. Discussion

We set out to reveal how reward seeking around foot shock and shock-associated cues changed as a function of experience. Measuring nose poke rate during cue presentation revealed a behavioural pattern our laboratory has previously observed with suppression ratios [31,33]. Reduced reward seeking to all cues in early sessions gave way to discriminative cue responding: danger < uncertainty < safety. Consistent with post shock freezing [25], early sessions were dominated by foot shock suppression of reward seeking that began immediately following shock offset and persisted thereafter. Post shock suppression diminished as fear discrimination continued, and was mostly confined to the first two seconds immediately following shock offset. Consistent with a prior report [19], foot shock facilitation of reward seeking emerged during later sessions. Facilitation was observed when foot shock was fully predicted on danger trials and was surprisingly delivered on uncertainty trials. Facilitation was rapid and transient, appearing as quickly as one second following shock offset and augmenting reward seeking for ~6s. Foot shock facilitation of reward seeking is a distinct behavioural mechanism, unrelated to the rate of baseline nose poking, degree of discrimination and degree of foot shock suppression.

Before discussing theoretical accounts and practical implications, several limitations must be raised. First, both the original demonstration of facilitation and the present experiment used male rats. The obvious question is if foot shock facilitation of reward seeking is observed in female rats. This work is underway in our laboratory and we speculate that female rats show foot shock facilitation of reward seeking. This is based on our observation that female rats readily acquire fear discrimination [37]. Further, manipulating shock-related prediction error activity - although a mechanism distinct from facilitation - has an equivalent effect on male and female fear behaviour [34]. We surmise that facilitation is a behavioural mechanism conserved across sexes. Second, our results demonstrate that foot shock facilitation of reward seeking is observed within our fear discrimination procedure. However, the full conditions that produce facilitation remain unknown. It is possible that we happened to select the exact parameters (cue duration, shock duration, shock intensity, inter-trial interval, etc.) to maximize the facilitation effect. In this case our results would not generalize well to other conditioned suppression procedures. Conversely, it is possible that we observed facilitation despite selecting non-optimal parameters. In this case, our results would underestimate the magnitude of the effect. Parametric studies are required to reveal the conditions that produce foot shock facilitation of reward seeking.

Various theoretical accounts have been offered to explain an increase in reward seeking following an aversive event. A compensatory account suggests that foot shock facilitation of reward seeking occurs as a result of subjects compensating for rewards 'lost' during previous suppression [20]. This is a plausible explanation for facilitated reward seeking following danger versus safety trials. Reward seeking is suppressed throughout the danger cue, but not the safety cue. Thus, greater reward seeking should be observed following shock delivery on danger trials to compensate for rewards 'lost' during cue presentation when reward

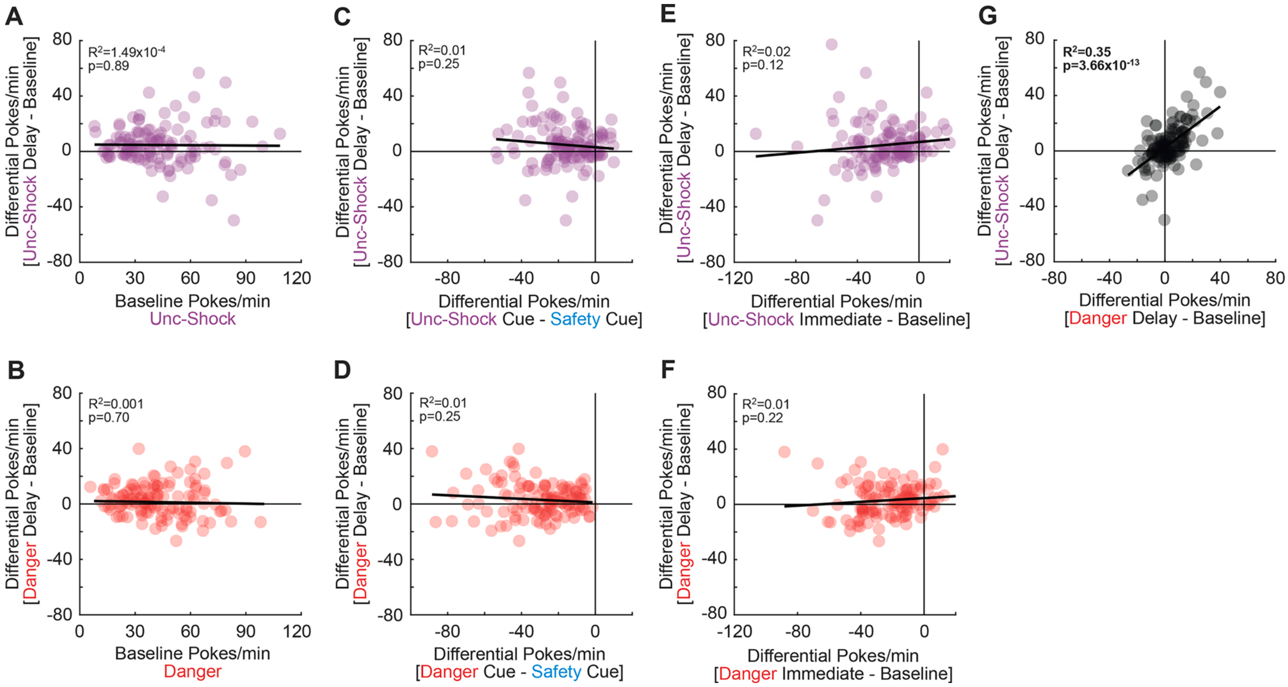

Fig. 5. Relationships between foot shock facilitation and other aspects of behaviour.
Mean differential nose poke rates for each subject during uncertainty-shock trials (uncertainty-shock minus baseline, upper panels), and danger trials (danger minus baseline, lower panels), compared to the baseline period (A–B), danger safety discrimination (danger minus safety, C–D), and immediate post shock period (immediate post shock minus baseline, E–F). Mean differential nose poke rates for each subject during uncertainty-shock trials (uncertainty-shock minus baseline, upper panels), and danger trials (danger minus baseline, lower panels), compared to one another (G).

seeking was suppressed. The compensatory account seems unable to explain facilitation of reward seeking following uncertainty-shock. Reward seeking is equally suppressed during the cue period for uncertainty-shock and uncertainty-omission trial types, yet facilitation is only observed during uncertainty-shock trials. If compensation alone drove post cue nose poking, then equivalent nose poking increases should have been observed following shock delivery and shock omission on uncertainty trials.

Another possible account is learned safety, in which a cue predicts the absence or omission of an aversive event [20,40–42]. It is plausible that in the current study, shock offset became associated with the absence of shock and this perhaps imbued shock offset with fear inhibiting properties. However, it is unclear how this would account for the transient period of facilitated reward seeking observed (~6s), when the actual shock-free period signaled by offset was far greater (2.5–3.5 min). Learned safety might anticipate a longer period of heightened reward seeking that decreased as the likelihood of the next foot shock increased. Indeed, this pattern can be observed when unsignalled foot shocks are presented in regular intervals over a baseline of reward seeking [30]. Even more, our procedure explicitly included a safety cue. If foot shock absence primarily drove nose poking increases, the largest increases should have been observed on safety trials. This did not occur, casting further doubt on the learned safety account.

Alternatively, the opponent process theory of acquired motivation can provide an adequate account of post shock increases in appetitive behaviour [19,43–45]. In opponent process theory, presentation of an aversive stimulus elicits a negative hedonic ‘a process’, followed by an opponent, positive ‘b process’. The hedonic state at a given time is the difference between the size of the ‘a process’ and ‘b process’ (a–b). Critically, the ‘a process’ rapidly engages at shock onset, peaks, and decays following shock termination. The ‘b process’ is initially weaker, engaged with a delay (relative to the ‘a process’), and slower to peak then decay following offset. With limited experience, the ‘a process’ will dominate. Continued experience with the aversive stimulus selectively and non-associatively strengthens the ‘b process’. This strengthening permits the ‘b process’ to outcompete the ‘a process’, particularly from its peak to decay. Strengthening of the hedonically positive ‘b process’ with continued experience can explain the transition from foot shock suppression to facilitation of reward seeking. Opponent process theory can also account for the transient nature of facilitation. Even though the ‘b process’ increases in strength, it will still decay and terminate shortly after it is engaged. As the ‘b process’ decays, reward seeking returns to baseline levels. Opponent process theory provides a reasonable explanation of the emergence of facilitation over discrimination and the time period during which facilitation is observed following foot shock.

A related mechanism that also develops over fear conditioning is conditioned analgesia, the process by which a shock-associated cue acquires the ability to dampen responses to nociceptive stimuli [46–48]. Conditioned analgesia and the hedonically positive ‘b process’ may be complimentary, but independent processes. Conditioned analgesia refers to a property acquired by a predictive cue, while the ‘b process’ refers to a property acquired by an aversive event. Conditioned analgesia requires associative learning, while strengthening of the hedonically positive ‘b process’ is theorized to be non-associative. Of course, our results cannot definitely conclude that foot shock facilitation of reward seeking was non-associatively acquired — foot shock was always predicted in our procedure. Still, our results, conditioned analgesia and even studies of conditioned diminution [68–70] suggest there is a suite of behavioural mechanisms that permit experience to minimize the impact of aversive events on behaviour. Associatively acquired conditioned analgesia may permit predicted aversive events to elicit weaker nociceptive responses. Associatively acquired conditioned diminution may permit inhibition of behavioural responses to well-predicted aversive events. Concurrently, non-associatively acquired positive hedonic properties of foot shock may rapidly promote a positive affective state to facilitate reward seeking.

An opponent process account also lends itself well to relief learning [49–55]. Relief learning is commonly obtained through backwards conditioning, in which foot shock predicts a cue with a 1–3s delay. Relief learning can endow a cue with inhibitory properties. For example, a backward conditioned cue can diminish startle, while a forward conditioned cue can potentiate startle [52]. The ‘event’ supporting inhibitory learning in backward conditioning is thought to be transient relief generated by the cessation of the painful stimulus. This phenomenological description of relief is similar to the positive hedonic state elicited by the ‘b process’ in opponent process theory. Although speculative, our results suggest that the hedonically positive, post shock signal that supports relief learning is sufficient to facilitate reward seeking on its own. Foot shock facilitation of reward seeking may be a form of general affective Pavlovian to instrumental transfer [56,57] that bridges appetitive and aversive motivational systems [58].

From a practical perspective, the transition from foot shock suppression to facilitation may be adaptive, capitalizing on the subject’s knowledge of the environment. When an aversive event is first experienced, it is impossible to predict if and when subsequent events will occur, much less the nature of those occurrences (number, duration, intensity, etc.). Engaging neurobehavioural systems for threat and negative affect may be adaptive, minimizing detection and further risk of harm. Continued experience may allow the subject to predict not just when an aversive event will occur, but the specific nature of its occurrence. Now it may be adaptive for termination of the aversive event to engage neurobehavioural systems for positive affect, facilitating reward seeking.

Associative learning has been a valuable tool in identifying adaptive behaviour that becomes maladaptive in stress and anxiety disorders. Fear discrimination and safety learning procedures have revealed altered behavioural responses to threat and safety cues in post-traumatic stress disorder [59–61]. Our results and extant findings suggest that studying behaviour around aversive events will be equally valuable [62,63]. Preclinical research can identify brain regions permitting foot shock facilitation. Relief learning studies have already identified critical roles for the ventral tegmental area and nucleus accumbens shell [51,52,64,65]. The mesolimbic dopamine system is perhaps likely to contribute to foot shock facilitation of reward seeking. Clinical studies can reveal experience-dependent changes in behaviour around aversive events. A straightforward hypothesis is that the suppression → facilitation transition normally observed for aversive events may be impaired in individuals with stress and anxiety disorders. Impairment could result from a failure to transition from aversive processing in nociceptive regions [66] to reward regions [49,67]. Of course, many more outcomes are possible. Revealing the neurobehavioural mechanisms underlying foot shock facilitation may allow us to harness the positive power of aversive events to promote adaptive behaviour.

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CRediT authorship contribution statement

JA Strickland: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **AD Dileo:** Data curation, Writing - review & editing. **M Moaddab:** Data curation, Writing - review & editing. **MH Ray:** Data curation, Writing - review & editing. **RA Walker:** Data curation, Writing - review & editing. **KM Wright:** Data curation, Writing - review & editing. **MA McDannald:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest.

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