Fear-potentiated startle

Differential FPS responding increased from the first to the last block of acquisition, cue x block interaction, $F(1, 56) = 48.19$, $p < .001$, $\eta_p^2 = 0.46$, with participants displaying greater startle amplitudes to the CS+ than to the CS- in the last acquisition block, $t(59) = 13.95$, $p < .001$ (see Figure 3). This pattern did not differ between the groups, group x cue x block interaction, $F(3, 56) < 1$, nor did it change when the CS+ was compared to the NA rather than the CS-, cue x block interaction, $F(1, 56) = 10.16$, $p = .002$, $\eta_p^2 = 0.15$; group x cue x block interaction, $F(3, 56) = 1.06$, $p = .37$, $\eta_p^2 = 0.05$. On the second day, memory retrieval was seemingly not successful, main effect of cue, $F(1, 42) = 2.80$, $p = .10$, $\eta_p^2 = 0.06$. A closer look revealed that statistically, only the PrPr group responded more to CS+ than NA during the retrieval session, $t(14) = 2.29$, $p = .04$, while the PrPl and PlPl groups did not, $t(14) = 1$, $p = .33$; $t(14) = 0.45$, $p = .66$, respectively. Nevertheless, unlike the PlPl group that showed an opposite pattern (NA > CS+), the PrPl group exhibited numerically higher responses to the CS+ ($M = 0.55$, $SD = 0.82$) than to the NA ($M = 0.27$, $SD = 0.84$).

On the first block of retention testing, contrary to our hypotheses, differential FPS was intact in all the groups, main effect of cue, $F(1, 56) = 13.09$, $p < .001$, $\eta_p^2 = 0.19$; group x cue interaction, $F(3, 56) < 1$, although the degree of differentiation decreased from the end of acquisition to the beginning of retention testing, cue x block interaction, $F(1, 56) = 56.31$, $p < .001$, $\eta_p^2 = 0.50$, similarly in all groups, group x cue x block interaction, $F(3, 56) < 1$. Follow-up analyses revealed that whereas CS+ responding increased only modestly, main effect of block, $F(1, 59) = 4.36$, $p = .04$, $\eta_p^2 = 0.07$, CS- responding increased more considerably, main effect of block, $F(1, 59) = 80.84$, $p < .001$, $\eta_p^2 = 0.58$, suggesting increased fear generalization to the safe stimulus with the passage of time. When the same analysis was repeated with the CS+ versus the NA, a significant group x cue interaction emerged, $F(3, 56) = 2.86$, $p = .045$, $\eta_p^2 = 0.13$. NA responding remained stable from the end of acquisition to the beginning of retention in the PrPr and PlPl groups, $Z = 49$, $p = .56$; $t(14) = 0.60$, $p = .56$, respectively, but increased in the PrPl and NR groups, $t(14) = 2.80$, $p = .01$; $t(14) = 3.54$, $p = .003$, respectively. Increased baseline startle amplitudes have been suggested to reflect greater general state anxiety (Poli and Angrilli, 2015). Note that the PrPl and NR groups scored higher numerically on the STAI-S at the beginning of retention, although this effect did not reach statistical significance, main effect of group, $F(3, 56) = 1.16$, $p = .33$, $\eta_p^2 = 0.06$.

The augmented CS- responding at the beginning of retention testing obscured the observation of differential extinction learning from the beginning to the end of the retention phase, cue x block interaction, $F(1, 56) < 1$; group x cue x block interaction, $F(3, 56) < 1$. However, when the CS+ was compared to NA, a significant extinction pattern emerged from the first to the last block, cue x block interaction, $F(1, 56) = 42.95$, $p < .001$, $\eta_p^2 = 0.43$; group x cue x block interaction, $F(3, 56) < 1$, suggesting that extinction had taken place. Of note, in both analyses, we observed a main effect of group, $F(3, 56) = 4.02$, $p = .01$, $\eta_p^2 = 0.18$; $F(3, 56) = 7.42$, $p < .001$, $\eta_p^2 = 0.29$, respectively, due to the PrPr group exhibiting diminished responding to all cues at both time points. To further examine whether extinction learning occurred, and to verify the attenuation of FPS in the PrPr group unconfounded by fear generalization at the beginning of retention testing, we compared the last block of acquisition with the last block of extinction and observed a decline in differential responding, cue x block interaction, $F(1, 56) = 45.36$, $p < .001$, $\eta_p^2 = 0.45$, that did not differ between the groups, group x cue x block interaction, $F(3, 56) < 1$, suggesting successful extinction. Further, we found a significant group x block interaction, $F(3, 56) = 2.99$, $p = .04$, $\eta_p^2 = 0.14$, and a main effect of group, $F(3, 56) = 3.48$, $p = .02$, $\eta_p^2 = 0.16$, pointing to weaker FPS responding during extinction in the PrPr group. To confirm those observations, the PrPr group was compared to each of the other three groups separately during the course of extinction. A group effect emerged in each of those comparisons, main effect of group, PrPr versus PrPl: $F(1, 28) = 4.59$, $p = .04$, $\eta_p^2 = 0.14$; PrPr versus PlPl: $F(1, 28) = 4.86$, $p = .04$, $\eta_p^2 = 0.15$; PrPr versus NR: $F(1, 28) = 8.59$, $p = .007$, $\eta_p^2 = 0.24$.

In the last block of the extinction phase, there were no group differences in the degree of differential responding, group x cue interaction, $F(3, 56) < 1$, but the PrPr group demonstrated an attenuation in their startle responding, whether considering CS+/CS- responding, main effect of group, $F(3, 56) = 4.00$, $p = .01$, $\eta_p^2 = 0.18$, or CS+/NA responding, main effect of group, $F(3, 56) = 6.38$, $p < .001$, $\eta_p^2 = 0.26$. Comparing the last block of extinction to the first trial of reinstatement, we saw a non-differential (cue x time interaction, $F(1, 56) < 1$) increase in responding to all cues, main effect of cue, $F(1, 56) = 5.97$, $p = .02$, $\eta_p^2 = 0.10$; main effect of time, $F(1, 56) = 79.04$, $p < .001$, $\eta_p^2 = 0.59$, in all groups, group x cue x time, $F(3, 56) < 1$; main effect of group, $F(3, 56) = 2.07$, $p = .12$, $\eta_p^2 = 0.10$.

In contrast to our hypothesis and to previous reports, propranolol administration after reactivation did not affect differential FPS responding during memory retention testing, nor

did it prevent reinstatement after extinction (PrPl group). We did observe an acute effect of propranolol administration on fear memory expression during extinction learning only, as the PrPr group exhibited attenuated startle responding throughout memory retention testing, yet similar sensitivity to reinstatement as the other groups.

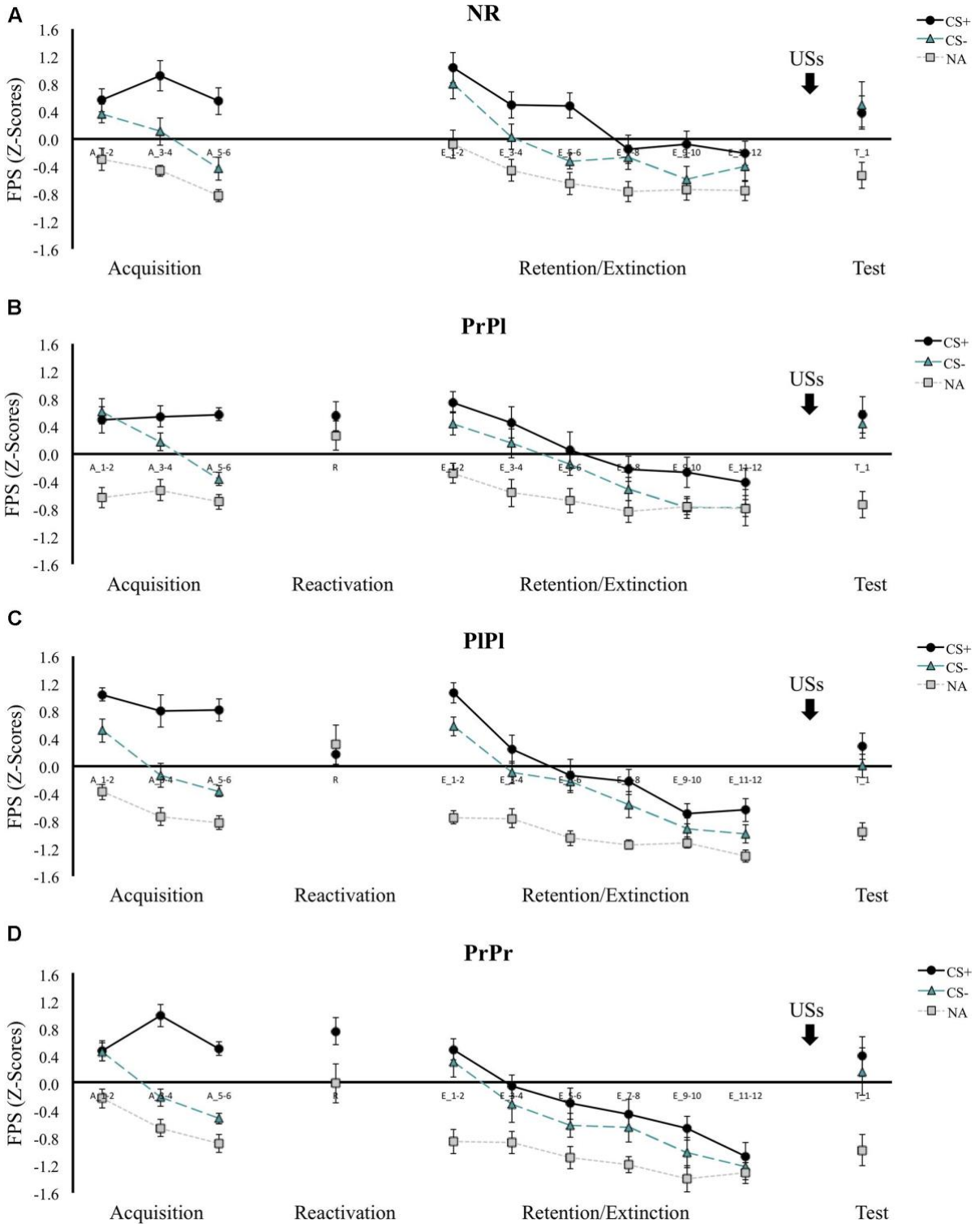

Figure 3. Mean FPS scores (*z*-transformed) across all phases for **(A)** the NR group, **(B)** the PrPl group, **(C)** the PlPl group, and **(D)** the PrPr group. Error bars represent standard error of the mean.