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Peripheral pain enhances the effects of incentive downshifts☆

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ABSTRACT

Physical pain (induced by tissue damage) and psychological pain (induced by surprising incentive loss) share a set of common neural substrates, but little is known about their interactions. The present research studied such interactions using the formalin test to induce physical pain and consummatory successive negative contrast (cSNC) to induce psychological pain. In the formalin test, animals receive an intradermal injection of formalin (1%) in a hind paw. In cSNC, rats with free access to 32% sucrose show a sharp suppression of drinking behavior after a downshift to 4% sucrose, compared to rats that always receive 4% sucrose. In Experiment 1, formalin administration before the first and second 32-to-4% sucrose downshift trials enhanced cSNC. In Experiment 2, a similar treatment before the first downshift trial after a 16-to-4% sucrose downshift, which normally produces little or no evidence of cSNC, significantly increased cSNC. In Experiment 3, using a 32-to-4% sucrose downshift procedure similar to that of Experiment 1, no effects were observed following formalin administration immediately after Trial 11. Thus, no evidence was found that the effects of physical pain on cSNC were caused by changes in memory consolidation. The procedures used in these experiments offer a new approach to study the neural substrates of interactions between physical and psychological pain.

Parallels between the effects on behavior of signals from physical pain (e.g., induced by electric shocks) and of signals from psychological pain (e.g., induced by incentive downshift) have been recognized since at least the 1950s (Amsel, 1958; Brown & Wagner, 1964; Gray, 1982; Wagner, 1963). For example, the presentation of signals paired with either shock-induced pain (Brown, Kalish, & Farber, 1951) or surprising incentive downshift potentiates the startle reflex induced by a loud noise in rats (Wagner, 1963). Based on results like these, Gray (1982) proposed a fear = frustration hypothesis according to which the same neural circuit underlies the emotional states that anticipate physical pain (fear) and incentive loss (anticipatory frustration).

Recent research has confirmed the extensive overlap between neural circuits and neurochemical systems underlying these two forms of pain (Eisenberger & Lieberman, 2004; MacDonald & Leary, 2005; Papini, Wood, Daniel, & Norris, 2006). In support of these findings, Mustaca and Papini (2005) trained rats in the consummatory successive negative contrast (cSNC) situation and then tested them in the hot plate situation. In the cSNC situation, rats that received daily access to 32% sucrose solution for 10 trials suppress their consummatory behavior when downshifted to 4% sucrose, relative to unshifted

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controls given only access to 4% sucrose. Such suppression is taken as an index of frustration (Papini et al., 2006). Mustaca and Papini (2005) also reported that paw-lick latencies in the hot plate test were increased (i.e., hypoalgesia) when animals were tested immediately after the second incentive downshift trial. Among the key neural structures activated by actual or anticipated physical pain and by situations involving incentive loss are the anterior cingulate cortex and the insular cortex (Abler, Walter, & Erk, 2005; Lin, Roman, & Reilly, 2009). Moreover, the opioid system participates both in the modulation of physical pain (e.g., Rochford & Stewart, 1987) and psychological pain induced by incentive downshift (e.g., Pellegrini, Wood, Daniel, & Papini, 2005).

The present experiments were designed to determine whether acute peripheral pain modulates consummatory behavior after an incentive downshift. In Experiment 1, acute pain was induced before the first and second postshift trials (Trials 11–12), after a 32-to-4% sucrose downshift event—the typical training parameters (e.g., Flaherty, 1996). In Experiment 2, a moderate disparity between pre- and postshift sucrose concentrations was used to determine whether acute pain induced before Trial 11 would induce a greater response to the incentive downshift event. A 16-to-4% sucrose downshift was used as it is known to yield little or no evidence of contrast (e.g., Papini & Pellegrini, 2006). In Experiment 3, acute pain was administered immediately after Trial 11 to determine whether its effects facilitate the consolidation of the emotional memory of the downshift event.

1. Experiment 1

The purpose of this study was to further explore the hypothesis that there is an interaction between physical and psychological pain. Experiment 1 used the formalin test (Dubuisson & Dennis, 1977) to induce an acute inflammatory physical pain condition. Formalin was injected subcutaneously into a hind paw before an incentive downshift from 32% to 4% sucrose (induction of frustration, or psychological pain) and in an unshifted control group given only access to 4% sucrose. Two additional groups, treated similarly in terms of the cSNC manipulation, received subcutaneous injections of saline solution. Therefore, the experimental design allows a distinction between the effects of formalin-induced physical pain on consummatory behavior after an incentive downshift versus after an unshifted incentive condition. If the effects of the formalin injection add to the effects of the incentive downshift, then the cSNC effect should be enhanced (a summation effect). If, however, the formalin effect attenuates the effects of the incentive downshift, then the cSNC effect should be ameliorated or even eliminated (an attenuating effect; see Mustaca & Papini, 2005).

1.1. Method

1.1.1. Subjects

The subjects were 36 male Long–Evans rats (Harlan, Indianapolis, IN), 90 days old at the start of the experiment, and experimentally naïve. Animals were gradually food deprived to 81–84% of their ad libitum weight over the course of 5–7 days and kept at this level during the course of the experiment. They were weighed daily and given supplementary food at least 15 min after the end of a training session. They were housed in individual wire-bottom cages with water freely available, in a colony room maintained under constant temperature and humidity. The colony was under a 12:12 h light:dark cycle (lights on at 07:00 h). Animals were trained during the light portion of the daily cycle, between the hours of 07:00 and 19:00.

1.1.2. Apparatus

Training was conducted in 4 conditioning boxes (MED Associates, St. Albans, VT) constructed of aluminum and Plexiglas, and measuring 29.4 cm in length, 28.9 cm in height, and 24.7 cm in width. The floor was made of steel rods 0.5 cm in diameter and 1.2 cm apart running perpendicular to the feeder wall. A bedding tray filled with corncob bedding was placed below the floor to collect fecal pellets and urine. Against the feeder wall was an elliptical perforation 1-cm wide, 2-cm high, and 3.5 cm from the floor. A sipper tube, 1 cm in diameter, was inserted through this hole. When fully inserted, the sipper tube was flush against the wall. A computer located in an adjacent room controlled the presentation and retraction of the sipper tube, and detected contact with the sipper tube by way of a circuit involving the steel rods in the floor. Each conditioning box was placed in a sound-attenuating chamber that contained a house light, a speaker to deliver white noise, and a fan for ventilation. Together, the speaker and fan produced noise with an intensity of 80.1 dB (SPL, Scale C)

1.1.3. Procedure

Each rat was randomly assigned to one of the conditioning boxes and always trained in that box. The order of training of the 4-rat squads varied across days. After each trial, conditioning boxes were cleaned with a damp paper towel, feces removed, and bedding material replaced as needed. During trials, the house light, white noise, and fan were on constantly. Animals received one trial per day, at approximately the same time every day; thus, the intertrial interval was approximately 24 h. Trials 1–10 were preshift trials, whereas Trials 11–14 were postshift trials. Prior to Trial 1, rats were matched by ad libitum weight and randomly assigned to the downshifted or unshifted condition. After Trial 10, downshifted rats were matched in terms of overall preshift performance and randomly assigned to one of the two conditions ($n = 9$): 32/Sal (saline) or 32/For (formalin). The unshifted controls were assigned likewise ($n = 9$): 4/Sal or 4/For.

For the two 32-to-4% groups (32/Sal, 32/For), the 10 preshift trials involved access to a 32% sucrose solution (w/w, prepared by mixing 32 g of commercial sugar for every 68 g of distilled water); the 4 postshift trials involved access to

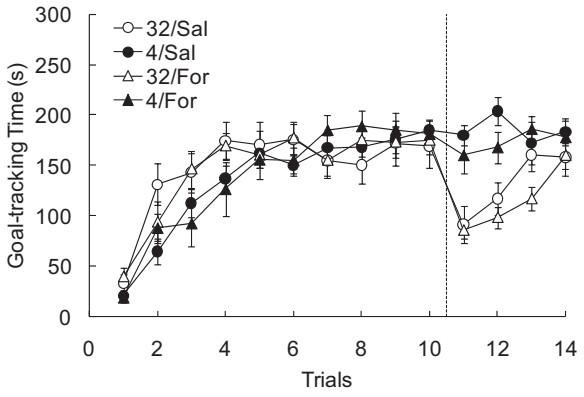

Fig. 1. Goal-tracking times for groups exposed to a 32-to-4% sucrose downshift (32) or 4-to-4% sucrose unshifted (4) conditions and given a saline injection (Sal) or formalin test (For) before Trials 11 and 12.

a 4% solution (w/w, 4 g of sugar for every 96 g of distilled water). The two 4-to-4% groups (4/Sal, 4/For) received the 4% sucrose solution in all 14 trials. Each trial started with a variable pretrial interval of 30 s (range: 15–45 s). At the end of this interval, the sipper tube was automatically presented. A trial started after the first detected contact with the sipper tube and lasted 5 min thereafter. Retraction of the sipper tube was followed by a posttrial interval averaging 30 s (range: 15–45 s). The dependent variable was the cumulative amount of time in contact with the sipper tube, measured in 0.05-s units, and labeled goal-tracking time.

Formaldehyde was purchased from Sigma–Aldrich Chemicals (Saint Louis, MO). It was freshly dissolved in isotonic saline solution to a 1% concentration and administered 12 min prior to Trials 11 and 12 into the plantar surface of a hind paw at a volume of 0.05 ml. No formalin injections were administered before any other trial. The 12 min time period was selected so that behavioral testing coincided with the beginning of the second phase of the formalin test (Dubuisson & Dennis, 1977). Saline animals received an equal-volume injection of isotonic saline. Right and left paws were alternated on Trials 11 and 12 (see LaBuda, Donahue, & Fuchs, 2001; LaGraize, Borzan, Rinker, Kopp, & Fuchs, 2004).

Goal-tracking times were subjected to conventional analysis of variance (ANOVA) and protected Fisher's LSD post hoc tests were used for pair wise comparisons among groups. The alpha value was set to $p < 0.05$ for all statistical tests. Similar to previous work (e.g., Wood, Norris, Daniel, & Papini, 2008), cSNC effects were evaluated by comparing downshifted versus unshifted groups given the same drug treatment (i.e., 32/Sal vs. 4/Sal and 32/For vs. 4/For). This comparison has the advantage of being consistent with the definition of cSNC, namely, the difference in performance between downshifted and unshifted groups. It also has the advantage that animals are equated by formalin treatment condition.

1.2. Results

The results are presented in Fig. 1. The results of the preshift phase were analyzed in a Contrast (32%, 4% sucrose) × Formalin (For, Sal) × Preshift Trial (1–10) design. Although formalin injections were not administered during the preshift trials, the factor was included to rule out biased assignment of animals. The overall analysis indicated a significant contrast by trial interaction, $F(9, 288) = 4.09$, $p < 0.001$, indicating that animals exposed to 32% sucrose acquired the goal-tracking response faster than animals exposed to 4% sucrose. There was also a significant increase of goal-tracking times across preshift trials, $F(9, 288) = 63.61$, $p < 0.001$. Other interactions and main effects were nonsignificant, Fs < 1. Therefore, no biases were detected as far as the assignment to the formalin/saline conditions.

A similar overall analysis for postshift trials (Trials 11–14) indicated a significant three-way interaction, $F(3, 96) = 3.02$, $p < 0.04$, as well as a significant contrast by trial interaction, $F(3, 96) = 8.33$, $p < 0.001$. Also significant were the main effects of contrast, $F(1, 32) = 21.10$, $p < 0.001$, and trials, $F(3, 96) = 11.69$, $p < 0.001$. Other effects failed to reach significance, Fs < 1.43, ps > 0.24. To determine de source of the triple interaction, two sets of pair wise analyses were calculated. First, groups equated by formalin treatment, but differing in their contrast treatment (downshifted vs. unshifted) were compared with each other on Trials 11–14. cSNC effects were found for Trials 11–12, Fs(1, 16) > 15.78, ps < 0.002, but not for Trials 13–14, Fs(1, 16) < 1.21, ps > 0.28, for Groups 32/Sal vs. 4/Sal. However, cSNC effects were significant for Trials 11–13, Fs(1, 16) > 14.17, ps < 0.003, although not for Trial 14, $F < 1$, for groups 32/For vs. 4/For. Therefore, the formalin treatment extended the cSNC by one trial.

Second, groups equated by contrast treatment, but differing in their formalin treatment (formalin vs. saline) were compared, again on Trials 11–14. Group 32/For scored significantly below Group 32/Sal on Trial 13, $F(1, 16) = 4.84$, $p < 0.05$, but the two were not differentiated on the other postshift trials, Fs < 1. Finally, Groups 4/Sal and 4/For were not different from each other in any of the trials, Fs(1, 16) < 2.95, ps > 0.10. Thus, formalin-induced peripheral pain affected consummatory behavior selectively in the group exposed to an incentive downshift. It is noteworthy that the effect of the formalin injection was detected on Trial 13, in which no formalin was administered.

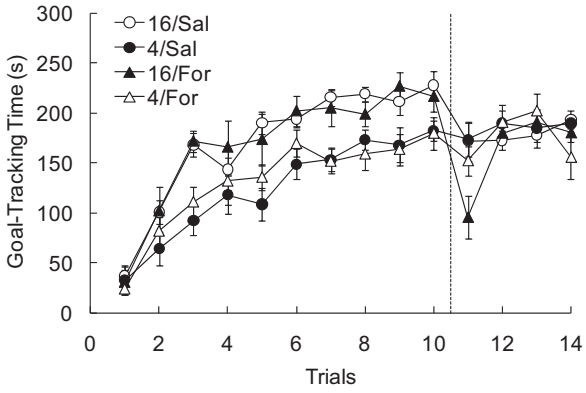

Fig. 2. Goal-tracking times for groups exposed to a 16-to-4% sucrose downshift (16) or 4-to-4% sucrose unshifted (4) conditions and given a saline injection (Sal) or formalin test (For) before Trial 11.

2. Experiment 2

The results of Experiment 1 suggest that physical pain induced by the formalin treatment added to the psychological pain induced by incentive downshift to significantly prolong the recovery from cSNC. Of additional interest is the finding that formalin treatment itself did not alter behavior in unshifted controls—Group 4/For. This outcome suggests that the effects of formalin-induced pain were specific to the incentive downshift event. Summation of hedonically aversive states directly induced by different sources (i.e., unconditioned effects) has not been commonly reported in the literature. However, examples of similar synergistic interactions involving aversive signals (i.e., conditioned effects) have been reported more frequently. For example, in fear-potentiated startle a signal previously paired with shock-induced peripheral pain enhances a startle reflex induced by a loud noise, in the absence of peripheral pain (Davis, 2007). Also, rats exposed to both shock and loud noise acquire an escape response faster when both sources are terminated by the animal's response than when only one of them is interrupted by the response (Myers, 1969). The summation hypothesis suggests that the effects of formalin-induced pain may combine with sub-threshold levels of psychological pain to induce a cSNC effect when none is normally observed. Therefore, in Experiment 2 rats were treated with formalin before a downshift from 16% to 4% sucrose. Such incentive disparity usually leads to less consummatory suppression compared to the greater disparity in the typical 32-to-4% sucrose downshift (Papini & Pellegrini, 2006).

2.1. Method

The subjects were 32 male Long–Evans rats, experimentally naïve, and 90 days old at the start of the experiment. They were housed and maintained as described in Experiment 1. Training took place in the conditioning boxes also described in Experiment 1. Animals were randomly assigned to four groups: Group 16/Sal ($n = 8$), 16/For ($n = 8$), 4/Sal ($n = 8$), and 4/For ($n = 8$). The procedure was also exactly as described in the previous experiment, with the following exceptions. First, animals were exposed to 16% and 4% sucrose solutions. The 16-to-4% sucrose downshift is known to produce significantly less consummatory suppression than the more typical 32-to-4% sucrose downshift (Papini & Pellegrini, 2006). The 16-to-4% disparity was chosen since it produces little or no evidence of cSNC and therefore directly tests the enhancement effects of peripheral physical pain on sub-threshold levels of psychological pain. The 16% sucrose solution was prepared by mixing (w/w) 16 g of commercial sugar for every 84 g of distilled water. Second, the number of injections was reduced from two to one to determine whether the effect could be obtained with the absolute minimum formalin stimulation. Third, the timing from the time of formalin injection to the beginning of behavioral testing was increased from 12 to 20 min to maximize the impact of the formalin treatment. This change was made since, although an effect of formalin on cSNC was detected in Experiment 1, there is a possibility that the effect was impacted by the interphase period of the formalin test. Dilute formaldehyde induces an initial period of responses (e.g., licking, elevation of injected paw) that persists to about 5–10 min after the injection. Such responses diminish and then fully return by 15–20 min after the injection (Dubuisson & Dennis, 1977).

2.2. Results

One animal in Group 16/For failed to develop consummatory behavior during the preshift trials and was hence withdrawn from the experiment (hence, $n = 7$ for that group). The results are presented in Fig. 2. Preshift trials indicated higher goal-tracking times for the groups given access to 16% sucrose than for those with access to 4% sucrose. A Contrast × Formalin × Preshift Trial (1–10) analysis indicated a significant contrast by trial interaction, $F(9, 243) = 2.60$, $p < 0.01$, and a significant main effect for contrast, $F(1, 27) = 16.43$, $p < 0.001$. There was also a significant increase across trials, $F(9,$

243) = 88.33, $p < 0.001$. Other effects were nonsignificant, Fs < 1. Therefore, no biases were detected as far as the assignment to the formalin/saline conditions.

As expected, a downshift from 16% to 4% sucrose did not produce evidence of cSNC in the groups treated with saline. Of primary importance is the finding that pretrial treatment with formalin led to a detectable cSNC effect on Trial 11. A similar analysis for postshift Trials 11–14 indicated significant interactions between contrast and trials, $F(3, 81) = 2.73$, $p < 0.05$, and formalin and trials, $F(3, 81) = 7.02$, $p < 0.001$. The three way interaction fell short of significance, $F(3, 81) = 2.33$, $p < 0.082$. There was also a significant change across trials, $F(3, 81) = 11.31$, $p < 0.001$. None of the main effects was significant, Fs < 1.33, ps > 0.26. Because the effect of the formalin test on cSNC was only appreciable on Trial 11, a second analysis was performed including only Trials 11–12. This time there was a significant contrast by formalin by trial triple interaction, $F(1, 27) = 5.43$, $p < 0.03$. Also significant were the formalin by trial double interaction, $F(1, 27) = 16.08$, $p < 0.001$, and the change across trials, $F(1, 27) = 28.17$, $p < 0.001$. Other effects were not significant, Fs < 2.45, $p > 0.12$.

To clarify the triple interaction observed for Trials 11–12, pair wise analyses were computed as done in Experiment 1, but only for these two trials. Equating groups in terms of drug treatment produced the following results. Groups 32/Sal vs. 4/Sal did not differ in either trial, Fs(1, 13) < 1.11, ps > 0.30, whereas Group 32/For vs. 4/For differed on Trial 11, $F(1, 13) = 5.07$, $p < 0.05$, but not on Trial 12, $F < 1$. Equating groups in terms of the contrast treatment showed that Group 32/Sal scored significantly above 32/For on Trial 11, $F(1, 13) = 7.10$, $p < 0.02$, but not on Trial 12, $F < 1$, whereas Group 4/Sal and 4/For did not differ on any of the trials, Fs < 1.

All together, the results of this experiment suggest that the addition of peripheral pain induced by formalin to a downshift disparity that usually produces little or no evidence of cSNC increased the size of the effect. Unlike in Experiment 1, however, the effect of formalin-induced pain on cSNC was restricted to the trial in which formalin had been administered (Trial 11).

3. Experiment 3

The results from Experiments 1 and 2 suggest that physical pain induced by formalin injection can summate with psychological pain induced by incentive downshift. Of primary importance is the finding that the presence of physical pain can induce a state of psychological pain when such a state is not normally detected. In addition, the effect of the formalin injection on cSNC was restricted to the same day of its administration in Experiment 2, but it was evident a day after its second administration in Experiment 1. These differences can be explained by at least two factors. First, the simplest explanation relies on the number of formalin injections administered: two in Experiment 1 and one in Experiment 2. Thus, it is possible that the extension of the cSNC effect in Experiment 1 was caused by two consecutive downshift trials performed under the influence of inflammatory pain. Second, the effect observed in Experiment 1 extended a day after the second formalin treatment. This suggests that a potential mechanism of action for the effect of physical pain on psychological pain is to facilitate the consolidation of the emotional memory of the incentive downshift. Several sources of evidence suggest that the downshift experience on Trial 11 results in the consolidation of an emotional memory. For example, posttrial 11 administration of corticosterone (Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006; Ruetti, Justel, Mustaca, & Papini, 2009) and D-cycloserine (Norris, Ortega, & Papini, submitted for publication) result in the subsequent enhancement of cSNC obtained after a 32-to-4% sucrose downshift. Therefore, Experiment 3 was designed to determine whether posttrial 11 formalin administration enhanced the subsequent development of the cSNC effect under conditions of training similar to those used in Experiment 1.

3.1. Method

The subjects were 31 male, experimentally naïve, Long–Evans rats, 90 days old at the start of the experiment. They were maintained and trained as described in Experiment 1, except that the formalin (or saline) injection was administered immediately after Trial 11. Animals were randomly assigned to Groups 32/Sal ($n = 7$), 32/For ($n = 8$), 4/Sal ($n = 8$), and 4/For ($n = 8$). Unequal group sizes were due to an insufficient number of available animals. All additional details of this experiment were as described in Experiment 1.

3.2. Results

The results are presented in Fig. 3. An analysis of preshift performance indicated a significant contrast by trial interaction, $F(9, 243) = 3.23$, $p < 0.002$, and significant main effects of contrast, $F(1, 27) = 21.83$, $p < 0.001$, and trial, $F(9, 243) = 44.42$, $p < 0.001$. All other effects were nonsignificant, Fs < 1. Thus, although all animals started at a similar level, rats exposed to 32% sucrose eventually exhibited higher goal-tracking scores than animals exposed to 4% sucrose. The results of the postshift analysis were similar. Again there were significant effects for the contrast by trial interaction, $F(3, 81) = 8.20$, $p < 0.001$, contrast, $F(1, 27) = 9.51$, $p < 0.006$, and trial, $F(3, 81) = 4.70$, $p < 0.005$. Other effects were nonsignificant, including those involving formalin treatments, Fs < 1.36, ps > 0.26. One-way analysis yielded significant effects for Trials 11 and 12, Fs (3, 27) > 6.37, ps < 0.003 (Trials 13–14: Fs < 1). On the two significant trials, the comparisons between each downshifted group (32/Sal and 32/For) and its respective unshifted control (4/Sal and 4/For) were significant, ps < 0.04. Thus, there was no evidence that posttrial formalin-induced pain enhanced the subsequent development of the cSNC effect.

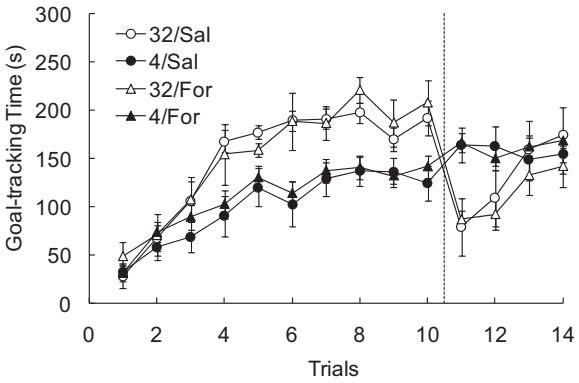

Fig. 3. Goal-tracking times for groups exposed to a 32-to-4% sucrose downshift (32) or 4-to-4% sucrose unshifted (4) conditions and given a saline injection (Sal) or formalin test (For) immediately after Trial 11.

4. General discussion

The purpose of these studies was to explore the hypothesis of an interaction between physical and psychological pain. The present results demonstrate that peripheral pain induced by intradermal injections of formalin into a hind paw administered before an incentive downshift event induce a more robust or longer-lasting reaction cSNC effect. This was demonstrated under the typical incentive downshift parameters (32-to-4% sucrose downshift; Flaherty, 1996) in Experiment 1 and also under conditions that do not usually generate a significant cSNC effect (16-to-4% sucrose downshift; Papini & Pellegrini, 2006) in Experiment 2. The latter effect highlights the additive nature of the effects studied in these experiments, as sub-threshold cSNC conditions become viable when compounded with preceding peripheral pain.

Little attention has been directed at the potential interactions between physical and psychological pain. A priori there are two potential interactions: (1) Summation: one emotional state enhances the other, or (2) Attenuation: one emotional state induces a compensatory response that reduces the other. Of the two possible outcomes, the present results support summation of physical and psychological pain states. The summation of physical and psychological pains, when administered in that order, indicates that the former increases the intensity of the latter. Such an increase in the intensity of psychological pain could play at least two roles in the cSNC situation: associative and nonassociative. An associative effect implies that the presence of physical pain facilitates the formation of an aversive memory of the downshift event. The results of Experiment 1 seemed to suggest such a possibility because the effects of formalin injections on Trials 11–12 were evident on Trial 13, when animals were not expressing behavioral signs of acute physical pain. However, other explanations are possible. For example, two pairings between the conditioning chamber and 4% solution with the development of physical pain could have supported fear conditioning; in turn, such fear conditioning may have suppressed drinking behavior in a manner analogous to the conditioned suppression of licking used in Pavlovian aversive situations (e.g., Doe, Nakajima, & Tamai, 2004). However, this explanation is inconsistent with at least two of the results reported here. First, such an effect should develop also in the unshifted controls, which showed no evidence of consummatory suppression on Trial 13 (or on any other trial). Second, Experiment 3 directly tested this hypothesis by administering the formalin test after Trial 11. Posttraining manipulations have been used traditionally to uncover factors that modulate memory consolidation (McGaugh, 2000). Posttraining drug administration has produce such effects in the cSNC situation (e.g., Wood et al., 2008), thus showing that the behavioral preparation has the potential to be sensitive to such manipulations. The negative results obtained in Experiment 3 cannot be dismissed on assumptions related to the size of the downshift, floor effects, or biased assignments.

Interestingly, the opposite sequence of training events, that is, when animals exposed to psychological pain (cSNC) were tested for physical pain sensitivity (hot plate test), has been found to result in an attenuation effect (Mustaca & Papini, 2005). In that experiment, exposure to the hot plate test immediately after Trial 12 in the cSNC situation (the second downshift trial) revealed a hypoalgesic response, relative to unshifted controls. The attenuating effect of psychological pain on physical pain (as in Mustaca & Papini, 2005) can be explained in terms of endogenous opioid release after incentive downshift. This explanation is consistent with the enhancement of cSNC by opioid blockage (Pellegrini et al., 2005), which suggests that an incentive downshift event normally induces release of endogenous opioids. Thus, rats exposed to incentive downshift undergo endogenous opioid release which then causes them to be hypoalgesic immediately after in the hot plate test. Physical pain induced by formalin is sensitive to *prior* treatment with opioid agonists like morphine and U50,488H, which induce hypoalgesia (Manning & Franklin, 1998; Pelissier, Paeile, Soto-Moyano, Saavedra, & Hernández, 1990). However, opioid blockage with naloxone *after* the formalin test has no effect on nociceptive behaviors (Kocher, 1988), suggesting that once initiated, pain induced in the formalin test is not modulated by opioid receptors. Although this evidence is consistent with the lack of attenuation of psychological pain (cSNC) by previous physical pain (formalin test) observed in the present experiments, it does not explain the observed summation effect.

The nonassociative explanation of summation of physical and psychological pains could be described as an emotional-motivational alternative akin to Hull's (1943) generalized drive notion. Incentive omissions analogous to what is implemented in the cSNC situation do occur in Pavlovian and instrumental procedures (Dudley & Papini, 1995; Stout, Boughner, & Papini, 2003). It seems plausible that behavior resulting from an experience of psychological pain is especially vulnerable to the invigorating effects of concurrent emotional changes (see Papini & Dudley, 1997). The combination of formalin test and cSNC opens a procedural door to explore the interactions between physical and psychological pains, as well as their underlying brain processes. These results have important theoretical implications for an understanding of the interaction between expectations and emotion, but also hold potential promise for the development of ideas for applied interventions in the areas of chronic pain and loss.

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