Report

Current Biology

Reducing Social Stress Elicits Emotional Contagion of Pain in Mouse and Human Strangers

Highlights

- Emotional contagion of pain in stranger mice can be elicited by stress reduction
- Emotional contagion of pain in cagemate mice can be blocked by stress
- Emotional contagion of pain in humans occurs in friends, but not strangers
- Stress reduction in humans can elicit emotional contagion of pain in strangers

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In Brief

Emotional contagion of pain can be observed, in both mice and humans, among familiar, but not stranger, dyads. Martin et al. show here that pharmacological or psychological stress reduction can elicit the phenomenon in stranger dyads. This suggests that stress is the key to emotional contagion, the fundamental building block of empathy.

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Report

Reducing Social Stress Elicits Emotional Contagion of Pain in Mouse and Human Strangers

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Summary

Empathy for another's physical pain has been demonstrated in humans [1] and mice [2]; in both species, empathy is stronger between familiars. Stress levels in stranger dyads are higher than in cagemate dyads or isolated mice [2, 3], suggesting that stress might be responsible for the absence of empathy for the pain of strangers. We show here that blockade of glucocorticoid synthesis or receptors for adrenal stress hormones elicits the expression of emotional contagion (a form of empathy) in strangers of both species. Mice and undergraduates were tested for sensitivity to noxious stimulation alone and/or together (dyads). In familiar, but not stranger, pairs, dyadic testing was associated with increased pain behaviors or ratings compared to isolated testing. Pharmacological blockade of glucocorticoid synthesis or glucocorticoid and mineralocorticoid receptors enabled the expression of emotional contagion of pain in mouse and human stranger dyads, as did a shared gaming experience (the video game Rock Band) in human strangers. Our results demonstrate that emotional contagion is prevented, in an evolutionarily conserved manner, by the stress of a social interaction with an unfamiliar conspecific and can be evoked by blocking the endocrine stress response.

Results and Discussion

Stress Affects Emotional Contagion of Pain Bi-directionally in Mice

We tested male mice for sensitivity to noxious stimuli in the abdominal constriction test either in isolation or in dyads in which both mice were injected with 0.9% acetic acid ("both in pain," or BP dyad condition; Figure 1A). Male mice tested in stranger dyads in which only one mouse received the noxious stimulus (and the other received a vehicle injection; "one in pain," or OP dyad condition) displayed naloxone-reversible (i.e., opioid-mediated) [4] stress-induced analgesia compared to isolated mice (Figure S1), as we have previously observed [2, 3], and were thus not appropriate as a control group. Mice were pretreated with the glucocorticoid synthesis inhibitor metyrapone, using the highest dose (50 mg/kg) producing no effect on pain behavior (see Figure S2A) in the isolated condition (t_{30} = 0.6, p = 0.53) (Figure 1A). Significant main effects of social context (isolated versus cagemate versus stranger: $F_{2,102}$ = 10.8, $p < 0.001$) and drug (vehicle versus metyrapone: $F_{1,102} = 10.7$, $p < 0.01$) and a significant interaction ($F_{2,102}$ = 3.3, $p < 0.05$) were obtained. In vehicle-treated mice, pain behavior in the dyadic condition increased significantly in cagemates (Tukey compared to isolated + vehicle, $p < 0.05$), but not strangers (p = 0.73), replicating our previous findings [2]. However, pretreatment with metyrapone significantly increased pain behavior in stranger dyads as well as cagemate dyads (Tukey compared to isolated + metyrapone, both $p < 0.05$) (Figure 1A). That is, metyrapone appeared to evoke, or allow, an empathic response (emotional contagion) between strangers normally observed only between cagemates. A higher dose of metyrapone (75 mg/kg) also elicited emotional contagion in a separate group of stranger dyads, while producing frank analgesia in isolated mice (Figure S2B). The effect of metyrapone was not affected by opioid receptor blockade, and these data were not confounded by locomotor activity, freezing behavior, or aggression, which did not differ between conditions (data not shown).

If stress reduction can elicit emotional contagion in strangers, the induction of stress might be expected to abolish the effect in cagemates. Cagemates simultaneously experiencing a 15-min restraint immediately prior to dyadic pain testing still exhibited hyperalgesia (isolated versus BP: t_{22} = 3.3, $p < 0.01$); however, after a 30-min restraint producing significant stress-induced analgesia (isolated groups only: $F_{2,33}$ = 4.3, $p < 0.05$), mice in the BP dyad condition displayed no trace of increased pain behavior (i.e., emotional contagion) (isolated versus BP: t_{22} = 0.6, p = 0.54) (Figure 1B).

Glucocorticoids act through two different receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). To determine the receptor(s) responsible for the metyrapone effect, we pretreated mice in a separate experiment (stranger dyads only) with the GR antagonist mifepristone (RU 486; 10 mg/kg), the MR antagonist RU 26752 (5 mg/kg), or a combination of the two drugs. None of these pretreatments affected pain behavior in mice tested in isolation (isolated drug groups only: $F_{3,50}$ = 0.4, p = 0.77). However, in the strangers-BP condition, the combination of mifepristone and RU 26752 significantly increased pain behavior (social context × drug: $F_{3,110} = 3.2$, $p < 0.05$) (Figure 1C), recapitulating the emotional contagion-evoking effect of metyrapone. Mifepristone alone was also ineffective at a higher dose of 20 mg/kg (data not shown). Taken together, these findings demonstrate that corticosterone acting at both GRs and MRs prevents emotional contagion of pain in stranger mice.

Since our previous demonstration of emotional contagion in mice [2], a number of studies have been published that are suggestive of empathy-related abilities in laboratory rodents and other non-primate species, including contagious yawn [5, 6], observational fear learning (via affect matching) [7–10],

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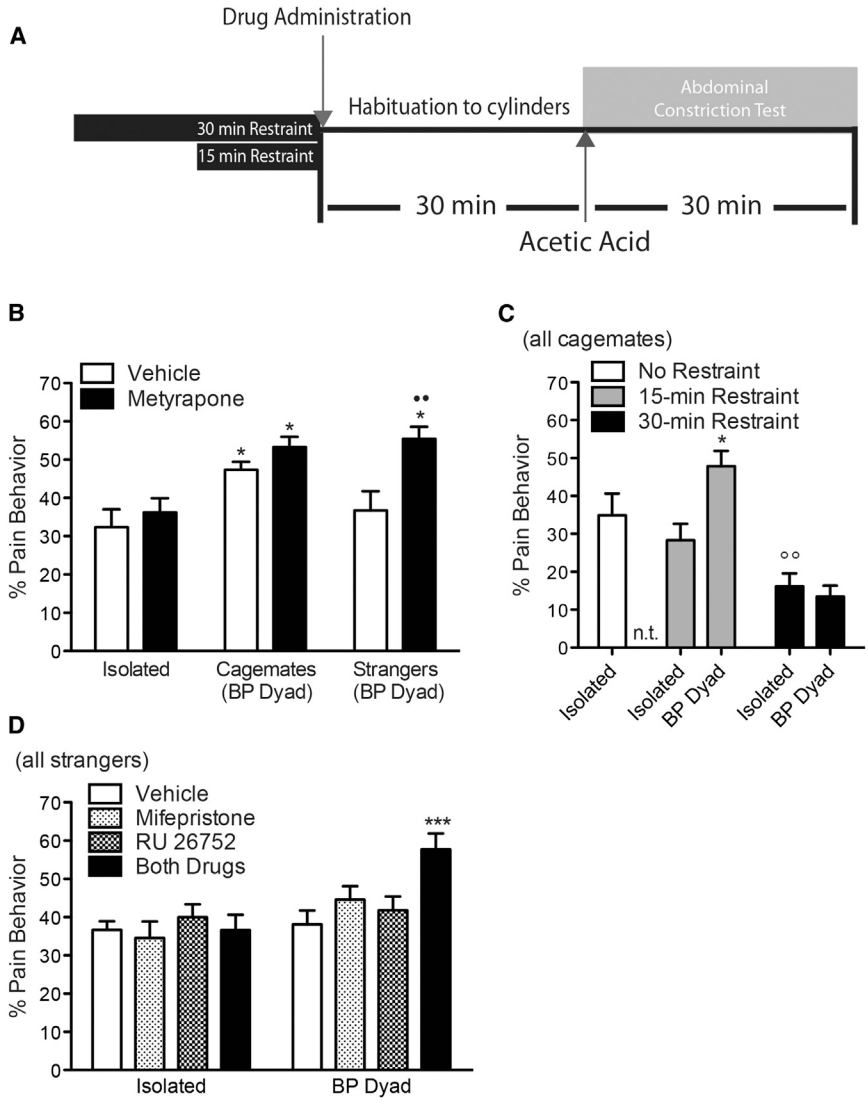

Figure 1. Modulation of Emotional Contagion by Stress in Laboratory Mice

(A) Experimental timeline. Note that unlike the human experiments, the mouse experiments were performed between subject, with mice assigned to only one drug or restraint group and to either Isolated, BP, or OP social conditions.

(B) Metyrapone (50 mg/kg), which does not affect pain behavior in mice tested in isolation or in cagemate dyads, elicits emotional contagion of pain in stranger BP ("both in pain") dyads otherwise only seen in cagemate BP dyads (n = 16–22 mice per social context per drug). OP ("one in pain") dyad data are presented in Figure S1. See Figure S2 for effects of higher metyrapone doses.

(C) 30 min, but not 15 min, of restraint stress abolishes emotional contagion of pain in cagemate BP dyads (n = 12 mice per condition). Note the duration-dependent pain inhibition (stress-induced analgesia) produced by 15- and 30-min restraint.

(D) A combination of the GR antagonist mifepristone (RU 486; 10 mg/kg) and the MR antagonist RU 26752 (5 mg/kg) enables emotional contagion of pain in stranger BP dyads, but has no effect on pain behavior in Isolated or OP conditions (n = 12–16 mice per social context per drug).

All bars represent mean ± SEM percentage of samples positive for abdominal constriction (pain) behavior in a 30-min period following the intraperitoneal injection of 0.9% acetic acid. *p < 0.05, ***p < 0.001 compared to analogous Isolated group(s) by one-way ANOVA followed by Tukey's post hoc test. ••p < 0.01 compared to analogous Vehicle group by t test. ○○p < 0.01 compared to analogous No Restraint group by one-way ANOVA followed by Tukey's post hoc test. n.t., not tested.

and prosocial (helping) behavior [11, 12]. Several reviews of this literature have recently been published [13–15]. Of direct interest are the observations made by Ben-Ami Bartal and colleagues (B.-A. Bartal et al., 2013, Society for Neuroscience Annual Meeting) that emotional contagion is required for helping behavior in rats (i.e., freeing a trapped and distressed conspecific) and that rats with lower corticosterone levels are more likely to engage in this behavior.

Humans Also Show Emotional Contagion of Pain

Although empathy for pain in humans is well studied [1], the emotional contagion effects we observe in mice have never been directly investigated using noxious stimuli applied to simultaneously tested human dyads. We recruited university undergraduates, some of whom were instructed to bring a same-sex friend with them to the experiment, whereas others were paired with a same-sex participant unknown to them, also scheduled to be tested the same day. Before any pain testing occurred, participants completed state mood measure (SMM) and pain catastrophizing scale (PCS) questionnaires (Figure 2A). Participants were then tested for sensitivity to noxious stimuli on the cold pressor test twice, in counterbalanced order, once alone and once silently facing a partner who was simply observing (OP dyad condition) or who was also being tested (BP dyad condition). Other than during dyadic pain testing, both participants were separated for the entire study. Dyadic testing was justified to participants with a ruse suggesting that it was a last-minute modification of the protocol necessitated by time pressures. After a 30-s immersion of the nondominant hand in 4°C water, participants were asked to rate pain intensity and unpleasantness on a 10-cm visual analog scale; these ratings were not visible to dyad partners. After all testing was completed, each participant completed questionnaires of dispositional empathy (interpersonal reactivity index, IRI) and feelings of friendship toward the other person tested. See Table S1 for demographic and questionnaire item effects in the isolated condition. Ratings of stimulus intensity and unpleasantness did not differ between groups when tested in isolation (all $p > 0.05$) in this and all subsequent experiments. However, as shown in Figure 2B, ratings of noxious stimulus intensity were significantly higher in friends-BP dyads compared to isolated testing (one-sample t test: $t_{16} = 3.4$, $p = 0.004$, Bonferroni-corrected $p = 0.02$); by contrast, ratings were not altered in strangers-BP dyads or in either OP dyad compared to isolated testing (all $p > 0.05$). The size of the increase was comparable in both male-male and female-female dyads (condition × sex interaction: $F_{1,39} = 0.3$, $p = 0.59$) in this and all subsequent experiments. These findings are highly

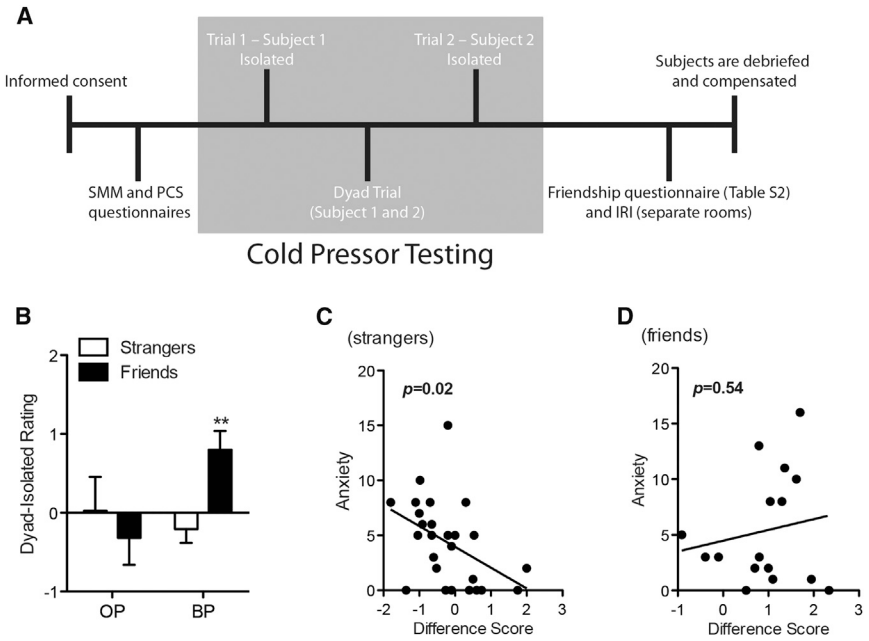

Figure 2. Human Friends, but Not Strangers, Demonstrate Emotional Contagion of Pain

(A) Experimental timeline.

(B) Emotional contagion of pain was observed in dyads if both participants were familiar and experienced pain together (BP), but not if participants were strangers or if dyadic testing involved only one participant in pain (OP). Bars represent mean ± SEM difference in pain intensity ratings between dyadic and isolated testing; n = 10–26 participants per condition. See Figure S3 for unpleasantness rating data.

(C and D) Significant correlation between self-reported anxiety and pain intensity difference scores (dyad-isolated) in BP strangers (C), but not in BP friends (D), indicative of stress-induced analgesia in the former. **p < 0.01 compared to analogous Strangers group by t test.

analogous overall to those observed in the mouse studies, except for the fact that no hypoalgesia was observed in human male OP dyads, likely because the fear of aggression was minimal in the context of a university laboratory study. In this and all subsequent experiments, no statistically significant main or interaction effects of gender or order of testing were observed, and similar results were obtained using unpleasantness ratings instead of intensity ratings (Figure S3). Correlations between questionnaire items and isolated-dyad rating change scores were investigated; the only similar correlations achieving statistical significance (uncorrected for multiple comparisons) were negative correlations between self-reported anxiety and pain intensity rating change in strangers ($r = -0.44$, $p < 0.05$) (Figure 2C), but not in friends ($r = 0.16$, $p = 0.54$) (Figure 2D), suggestive of stress-induced analgesia in the strangers only.

The present findings are unlikely to be due to social support or buffering (i.e., the mere presence of a friend) [16] since buffering would be expected to operate as well or better in the OP dyads, where, in fact, no effects on pain were observed. Social buffering of experimental pain in humans has been demonstrated [17, 18] but is highly context dependent [19], and solicitous partners have been shown to worsen pain [20, 21]. We are unaware of any existing studies similar to our BP dyads, in which two human participants are tested for pain sensitivity simultaneously. Most existing studies of pain empathy in humans have involved visual stimuli (pictures, video, or arbitrary cues) presented to a single participant [22–27].

Metyrapone Pretreatment Enables Emotional Contagion in Human Strangers

Based on findings in the mouse, we repeated the experiment described above using stranger dyads only, but with all participants pretreated with either 750 mg oral metyrapone or placebo 60 min before the first pain test. The experimental procedure was identical to that described above except that saliva samples were obtained before and after pain testing, and subjects were covertly videotaped for later analysis (Figure 3A). As shown in Figure 3B, strangers given metyrapone, but not placebo, reported significantly increased stimulus intensity compared to isolated testing ($t_{18} = 3.6$, $p = 0.002$, Bonferroni-corrected $p = 0.008$); ratings were not altered in placebo-BP dyads or in either OP dyad (all $p > 0.05$). This increased pain sensitivity in metyrapone-BP dyads occurred despite the fact that this dose of metyrapone produced a hypoalgesic effect in participants when tested alone ($t_{61} = 2.4$, $p < 0.05$) (Figure 3C). Thus, as in mice, blocking the endocrine stress response elicited emotional contagion of pain in strangers. Analysis of saliva samples confirmed the reduction of cortisol levels by metyrapone compared to placebo ($t_{35} = 2.8$, $p < 0.01$) (Figure 3D). Videotape analysis of pain testing by coders blinded to drug condition revealed that in metyrapone-treated subjects, but not placebo-treated subjects, there was a significantly greater number of painful facial expressions and post-testing pain behaviors (hand touching and holding) in the BP dyadic condition versus the isolated condition ($t_{25} = 2.2$, 2.1, and 2.2, respectively; all $p < 0.05$) (Figure 3E), providing further behavioral evidence of the effect of stress reduction on emotional contagion of pain.

Although the neuroanatomical basis of empathy for pain is now well characterized [28], the neurophysiology and neurochemistry of empathy remain obscure. The present study suggests for the first time that the hypothalamic-pituitary-adrenal stress axis is an important modulatory system. The effects of stress on emotional contagion appear to be mediated by both high-affinity MRs, known to mediate the effects of basal glucocorticoids, and the lower-affinity GRs, which predominantly mediate signaling by stress-induced increases in glucocorticoid levels [29]. In fact, MRs exhibit such a high affinity for glucocorticoids that most of these receptors are constantly occupied, even during periods of low basal release [30]. Thus, it was surprising that an acute stress-related phenomenon involved MRs since GR activation was presumably sufficient. Both MRs and GRs are typically regarded as intracellular receptors; emerging evidence indicates that MRs can also be positioned on the membrane of limbic region neurons, where they possess GR-like corticosterone affinity and drive fast signaling cascades [31]. Membrane-bound MRs have been shown to be relevant for acute stress-related effects on memory [32] and aggression [33].

It has been reported that intranasal oxytocin (and oxytocin receptor gene variants) affect both stress and various

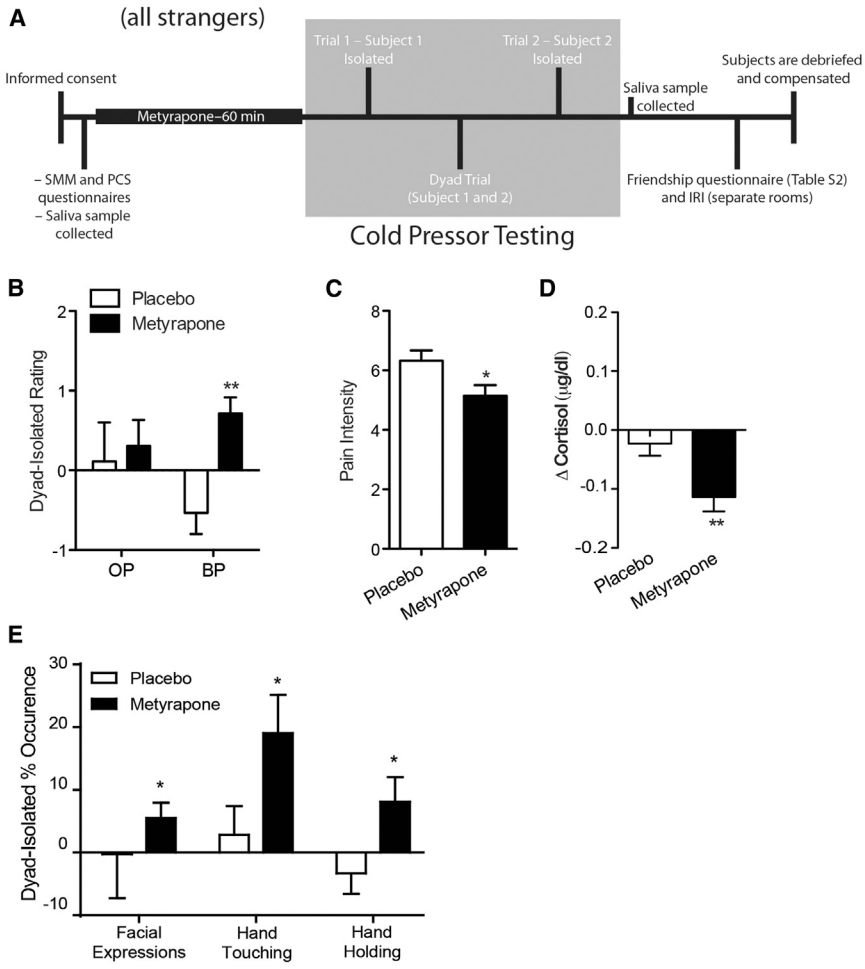

Figure 3. Metyrapone Elicits Emotional Contagion of Pain in Human Strangers

(A) Experimental timeline. See Figure S4 for an identically performed experiment using intranasal oxytocin.

(B) Emotional contagion of pain in stranger BP dyads where both participants have been pretreated with metyrapone. Bars represent mean ± SEM difference in pain intensity ratings between dyadic and isolated testing; n = 11–20 participants per condition.

(C) Metyrapone (750 mg) produced analgesia per se, in participants tested in isolation. Bars represent mean ± SEM in pain intensity ratings of all participants during isolated testing.

(D) Metyrapone significantly decreased cortisol levels. Bars represent mean ± SEM change in plasma cortisol.

(E) Facial expressions and pain-related behaviors of BP dyad participants captured by a video camera for 30 s following removal of the arm. Bars represent mean ± SEM dyad-isolated difference in occurrence of behaviors as a percentage of total observation time. *p < 0.05, **p < 0.01 compared to analogous Placebo group by t test.

components of empathy in humans [34–37], albeit in a complex manner [38]. We attempted to replicate the human metyrapone experiment using intranasal (24 IU) oxytocin and found no significant effects of oxytocin on pain contagion. Also, oxytocin in our hands did not produce any reduction in cortisol levels (Figure S4).

A Shared Social Experience Enables Emotional Contagion in Human Strangers

It is likely that in both mice and humans, the stressor preventing the emergence of emotional contagion is related to the forced social interaction between strangers in a novel environment because all other test-related stressors in both species are equivalent across conditions. We thus reasoned that we might be able to diminish this social stress directly in humans by having strangers engage in a social bonding activity immediately prior to dyadic pain testing. To this end, we repeated the original experiment but added a brief, between-subject social or non-social pleasurable experience whereby participants (all strangers) "played" four well-known songs by The Beatles in the video game Rock Band (Figure 4A). Half of the participants played the game alone, whereas half played together in a cooperative game mode in which the players' game score is based on joint performance. As shown in Figure 4B, only those who played together demonstrated the emotional contagion effect of increased stimulus intensity ratings in BP-dyadic versus isolated testing (t_{15} = 3.3, p = 0.005). Moreover, the size of the effect correlated significantly with self-report indices of trust or comfort with the stranger (r = 0.55, p < 0.05) (Figure 4C). The cooperative gaming experience also decreased plasma cortisol levels similarly to metyrapone (t_{36} = 2.4, p < 0.05, compared to playing alone) (Figure 4D). Finally, significant changes in the inclusion of other in the self (IOS) scale of interpersonal closeness (t_{37} = 2.8, p < 0.01) and the amount of money offered to the stranger in the dictator game (t_{37} = 2.0, p < 0.05) demonstrated that playing the video game together increased affiliation (Figures 4E and 4F).

Conclusions

Here, we replicate our previous findings that emotional contagion of pain occurs between familiar, but not stranger, mice and extend those findings to humans. The translation between species was surprisingly direct, with effects of similar magnitude demonstrated using similar sample sizes. The current demonstration that emotional contagion is readily translatable from mice to humans provides an excellent opportunity to exploit mouse genetics and physiology to better understand underlying mechanisms of the phenomenon, on which higher forms of empathy are dependent [39].

That a form of empathy would be present only in cagemates and friends is directly predicted by the perception-action model of empathy [39], which posits that empathy increases with both familiarity (subject's previous experience with object) and similarity (perceived overlap between subject and object). A recent study in mice observed that familiar observers freeze more than strangers when witnessing another mouse being shocked [40]. It was also shown recently that cortical activation patterns of pain-related (electric shock) threat to the participant correlated with patterns associated with the same threat to an opposite-gender friend, but not to a stranger [41].

We are unaware of any prior demonstration or speculation that stress can directly affect emotional contagion, although

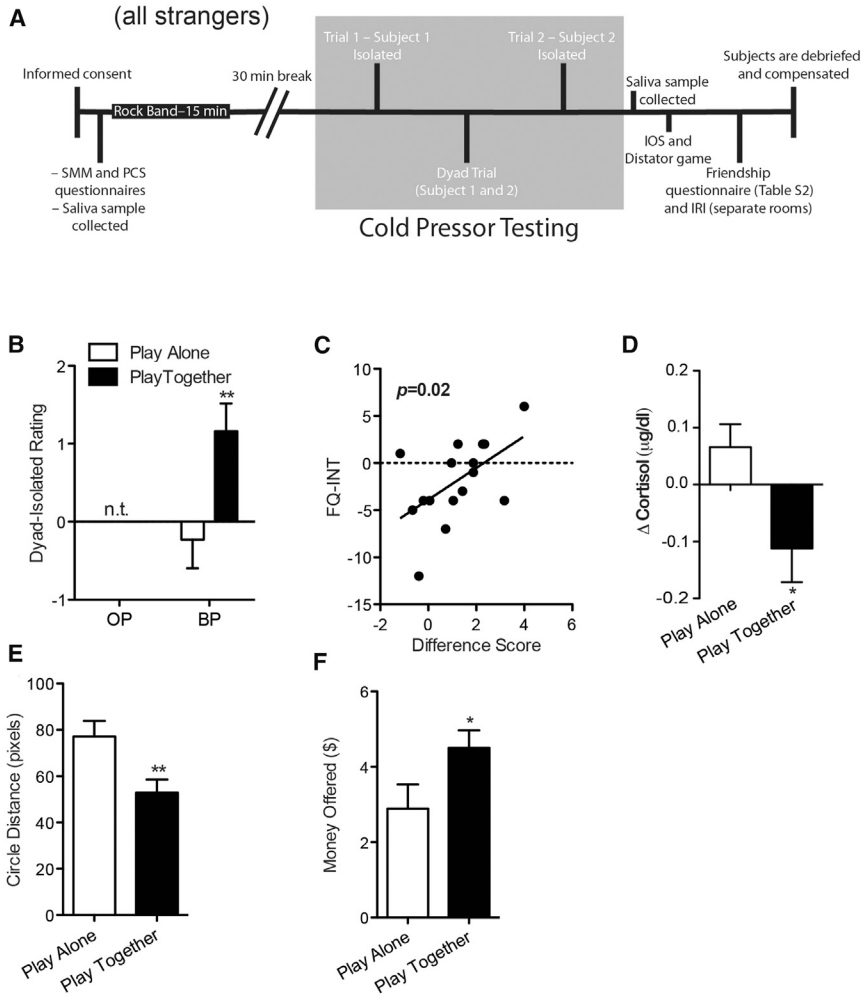

Figure 4. A Shared Gaming Experience Elicits Emotional Contagion of Pain in Human Strangers

(A) Experimental timeline.

(B) Emotional contagion of pain in stranger BP dyads having shared a brief pleasurable social experience (playing the Rock Band video game together); no effect was produced by playing the video game alone. Bars represent mean ± SEM difference in pain intensity ratings between dyadic and isolated testing; n = 15–16 participants per condition.

(C) Significant correlation between friendship questionnaire intimacy (FQ-INT) scores and pain intensity difference scores (dyad-isolated).

(D) Playing Rock Band together decreased cortisol levels. Bars represent mean ± SEM change in plasma cortisol.

(E and F) Playing Rock Band together increases two measures of interpersonal affiliation. In the inclusion of other in the self (IOS) scale of interpersonal closeness (E), participants move circles labeled "self" and "other" to overlap each other to the degree most resembling their relationship with the other individual. Bars represent mean ± SEM distance between the center of the circles. In the dictator game (F), both participants were told (separately) that they were chosen to receive an extra $10 compensation for the experiment, any portion of which they could donate to the other participant who would otherwise receive nothing. Bars represent mean ± SEM money offered. *p < 0.05, **p < 0.01 compared to analogous Play Alone group by t test. n.t., not tested.

it has been shown that (1) stress itself can be directly contagious [42], displaying physiological resonance between individuals; (2) empathy for negative emotions, including stress, can be stressful to the empathizer [42, 43]; and (3) acute psychosocial stress can reduce ratings of the pain of others [44]. The present demonstration that stress can impair emotional contagion in familiar mice and that stress reduction can enable it in stranger mice and humans raises the tantalizing possibility that higher forms of empathy are similarly controlled. If so, simple and readily achievable strategies for increasing empathic behavior among strangers in specific contexts are suggested, as are strategies for increasing empathy in the context of chronically stressed relationships. Some recent experiments have demonstrated that social stress can increase prosocial behaviors in humans, such as trust and sharing [45]. We suggest that the apparently divergent effects of stress observed here may reflect the different components of empathy that have been studied (emotional contagion versus prosocial helping) and/or differences in how stress is construed ("threat" or "challenge" [46]). That is, social stress could generally prevent individuals from sharing a stranger's pain, but there may be circumstances that override this effect, and the metabolic effects of acute stress can then be marshalled to benefit real, prosocial action; for example, when the need is clear, a helpful response is available, and the helper feels confident and efficacious [46].

Experimental Procedures

Mouse Experiments

Behavioral experiments were performed on young adult male, CD-1 mice. Nociceptive sensitivity was assessed using the 0.9% acetic acid abdominal constriction test, under three social conditions: (1) in isolation, (2) in OP dyads where one mouse received intraperitoneal acetic acid and the other saline, or (3) in BP dyads where both mice were injected with acetic acid. In dyadic conditions, mice were drawn from either the same home cage (cagemates) or different home cages (strangers). Mice were pretreated with systemically delivered drugs 30 min prior to acetic acid injection. In some experiments, mice were restrained in conical tubes for 15 or 30 min prior to habituation.

Human Experiments

Participants were McGill undergraduates recruited to the experiment either individually or in friend pairs. Pain testing using the 4°C cold pressor test occurred twice, in counterbalanced order, once alone and once directly across from either a friend or a stranger. After a 30-s immersion in the cold water, participants privately provided intensity and unpleasantness ratings on a visual analog scale. In one experiment, face and hand gestures were recorded by video and coded subsequently by blinded observers. Stress levels at various time points in the experiment were measured via salivary cortisol, and mood, catastrophizing, trait empathy, and friendship were measured via questionnaires. Affiliation was measured using the IOS scale and the dictator game. In one experiment, stranger participants were pretreated with either 750 mg metyrapone or a placebo pill. In one experiment, stranger participants were pretreated with either intranasal oxytocin (Syntocinon; 24 IU) or placebo inhalation. Finally, in one experiment, participants played the video game Rock Band either alone or with another (stranger) participant.

Statistics

Data were analyzed (Systat v.13) using Pearson's correlation coefficient, Student's t test, or ANOVA, followed, where appropriate, by post hoc testing

using Tukey's or Dunnett's case-comparison test. A criterion α level of 0.05 was used in all cases.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, four figures, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2014.11.028.

Author Contributions

R.M.S. and J.S.M. conceived of the study. L.J.M., J.A.B., D.J.L., and J.S.M. designed the study. L.J.M., G.H., K.I., S.M., E.L.A., N.N., P.M.S., and W.F.S. performed the study. L.J.M., Z.T., W.F.S., and J.S.M. analyzed the data. L.J.M. and J.S.M. wrote the manuscript, with input from all the authors.

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