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Dale J. Langford, *et al.*
Science **312**, 1967 (2006);
DOI: 10.1126/science.1128322

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sidering the actually imposed changes in leg length) that ants might run by as much faster on stilts as they ran slower on stumps (0.48 m/s, a value regularly observed in highly motivated normal ants and almost reached by the fastest ants on stilts). This procedure indeed yields a value that is not significantly different from the observed homing distances in ants on stilts (open box in Fig. 3, A; 14.25 m, IQR = 3.35 m), thus confirming the consistency of our data with the step integrator hypothesis.

The slower speeds of the ants walking on stilts further rule out the only alternative explanation of our homing distance data (Fig. 3A, solid boxes). In principle, a step integrator and a time-lapse integrator would both yield the same homing distances, even in ants with manipulated leg and stride lengths, if only the ants kept their stride frequencies constant [or in normal ants, walking speed—which in fact they almost do under normal conditions (19, 20)]. Constant stride frequency would result in a change in walking speed in proportion to altered stride length and a resulting difference in homing distance during a set (outbound) travel time. This assumption is evidently

not correct, though, given the walking speeds of the experimental animals.

Future studies will have to address the mechanism of the proposed step integrator, for example, whether it actually registers steps by means of proprioceptors, or whether it integrates activity of a walking pattern generator, and to what extent sensory feedback regarding stride length and walking performance is considered.

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- Funded by the Volkswagen Stiftung (I/78 580 to H.W. and R.W.), the Swiss National Science Foundation (3100-61844 to R.W.), and the Universities of Ulm and Zürich.

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2 March 2006; accepted 26 May 2006
10.1126/science.1126912

Social Modulation of Pain as Evidence for Empathy in Mice

Dale J. Langford, Sara E. Cramer, Zarrar Shehzad, Shad B. Smith, Susana G. Sotocinal, Jeremy S. Levenstadt, Mona Lisa Chanda, Daniel J. Levitin, Jeffrey S. Mogil*

Empathy is thought to be unique to higher primates, possibly to humans alone. We report the modulation of pain sensitivity in mice produced solely by exposure to their cagemates, but not to strangers, in pain. Mice tested in dyads and given an identical noxious stimulus displayed increased pain behaviors with statistically greater co-occurrence, effects dependent on visual observation. When familiar mice were given noxious stimuli of different intensities, their pain behavior was influenced by their neighbor's status bidirectionally. Finally, observation of a cagemate in pain altered pain sensitivity of an entirely different modality, suggesting that nociceptive mechanisms in general are sensitized.

Although most consider true empathy to be an exclusive ability of higher primates, empathy may be a phylogenetically continuous phenomenon with subclasses such as “emotional contagion” well within the reach of all mammals (1). However, there is little evidence for adult-adult empathy outside of primates. In rats (2) and pigeons (3), the pain-related distress of a conspecific can serve as a conditioning stimulus. Rats produced operant responses to terminate the distress of a conspecific (4), but this might be better explained by arousal than altruism (5). One theory of human empathy postulates “physiological linkage” between empathizing individuals (6).

In one study, empathic accuracy for negative emotion was highest in those dyads featuring high levels of time synchrony of autonomic measures (7). We hypothesized that if empathy does indeed exist in mice, the real-time observation of pain in one mouse might affect the responses of its conspecifics to painful stimuli.

We first used a sensitive nociceptive assay, the reflexive 0.9% acetic acid abdominal constriction (“writhing”) test. We placed mice singly within transparent Plexiglas cylinders to observe writhing behavior. For comparison, we placed two same-sex mice within each cylinder and injected either one or both mice. In the “both writhing” (BW) condition, each mouse observed the other in pain; in the “one writhing” (OW) condition, the injected mouse observed an uninjected counterpart. BW mice displayed significantly more pain behavior than isolated mice, but only when their counterparts

were cagemates (Fig. 1A). The hyperalgesia was marginally enhanced in same-sex siblings living together, but a separate experiment confirmed that close genetic relatedness was not required (fig. S1). Writhing behavior in BW dyads co-occurred in time at levels significantly exceeding those expected by chance (Fig. 1B) and significantly more so in cagemate pairs than stranger pairs. The hyperalgesia and behavior co-occurrence developed over 14 to 21 days of being housed together (Fig. 1, C and D). In general, observed behaviors other than writhing were similar across all conditions (figs. S2 and S3), although evidence suggested higher levels of anxiety or stress produced by the noxious stimulus in stranger pairs relative to cagemates (fig. S4). Because the observed effects on pain behavior were higher in cagemates, stress is not a likely mediator.

When strangers were tested in dyads, a significant decrease in writhing behavior was observed in the OW condition compared to that observed in isolation (Fig. 1A). The inhibition was entirely specific to males (fig. S5) and is likely due to distraction or social stress-induced analgesia.

These findings imply the communication of pain from one mouse to another. To determine the transmitting sensory modality, we blocked sensory inputs individually, by placing physical barriers to sight and/or touch or by rendering mice anosmic or deaf (8). The only manipulation that significantly abolished the BW/OW hyperalgesia was a visual blockade using an opaque Plexiglas barrier (Fig. 2A). [Despite their albinism, the CD-1 mice used in these studies display no deficits in visually dependent behavioral tasks (9).] The opaque barrier also

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Fig. 1. (A to D) Mice injected with 0.9% acetic acid in the presence of similarly injected cagemates display higher levels of pain behavior, which co-occurs in time. In all graphs, group sample sizes are indicated in italics. (A) Mice were tested in isolation (Isolated), or in dyads where either one mouse (One Writhing; OW) or both mice (Both Writhing; BW) received acetic acid injections. Bars represent the mean \pm SEM percentage of sampled intervals showing writhing behavior (% Samples Writhing). * $P < 0.05$, *** $P < 0.005$ by Dunnett two-way case-control comparison posthoc test compared to Isolated mice. (B) Statistically significant co-occurrence in writhing behavior in the Cagemates and Strangers conditions (sign test, $P < 0.05$ in both cases); the co-occurrence was significantly higher in Cagemates. Using data from (A), the expected number of samples with writhing in both mice of the dyad was calculated as a joint probability. Bars represent the mean \pm SEM excess of observed samples with joint writhing above the expected value, as a percentage. ** $P < 0.01$ compared to Strangers (Student's t test). (C) Data from a separate experiment using naïve mice housed together for 1, 7, 14, 21, or 28 days and tested in BW dyads. Isolated mice were taken from the 28-day group, but were tested alone. Bars are as in (A). * $P < 0.05$ by Dunnett one-way case-control comparison posthoc test compared to Isolated mice. Data in (D) were calculated from subjects shown in (C); symbols represent the mean \pm SEM excess of observed samples with joint writhing above the expected value, as a percentage. * $P < 0.05$ compared to zero (sign test). Significant linear trends were evinced in (C) and (D) ($P = 0.001$ and $P < 0.005$, respectively).

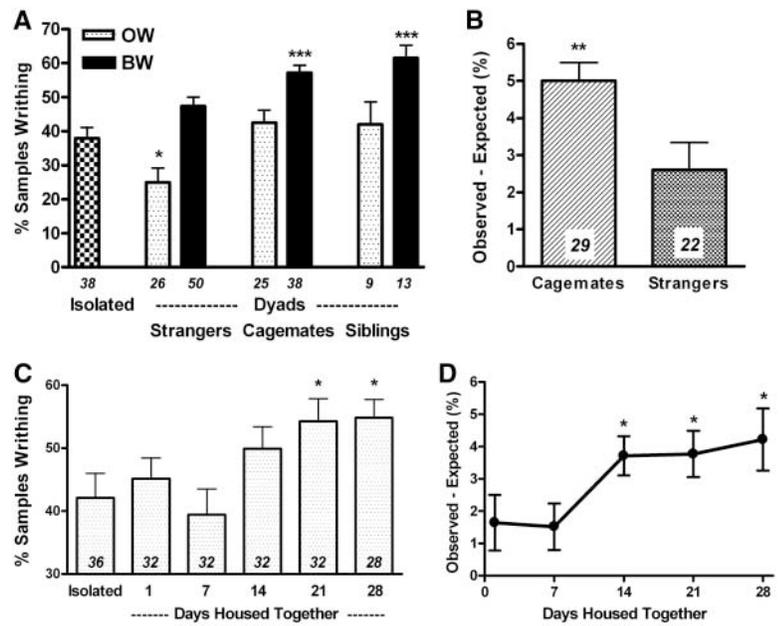
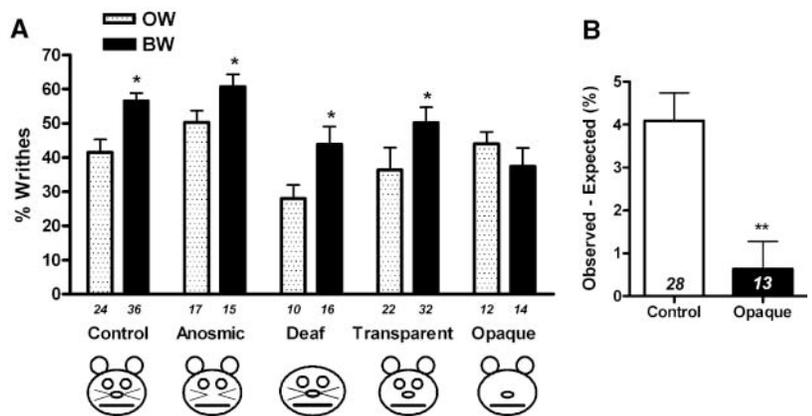


Fig. 2. (A and B) Apparent dependence of socially mediated hyperalgesia and co-occurrence on visual cues. Mice, all cagemates ($n = 10$ to 36 per group; housed together for >21 days), were tested in dyads as described in Fig. 1, such that either one mouse (One Writhing; OW) or both mice (Both Writhing; BW) received 0.9% acetic acid injections. "Control" data (intact mouse face cartoon) were taken from Cagemates condition in Fig. 1 for purposes of comparison. (A) Bars represent the mean \pm SEM percentage of sampled intervals showing writhing behavior (% Samples Writhing). * $P < 0.05$ by Student's t test compared to OW group. The significantly lower writhing behavior of the Deaf-OW group reflects the relative insensitivity to the noxious stimulus of the BALB/c strain, as previously reported (24). (B) The abolition of writhing behavior co-occurrence in BW dyads in which one mouse is prevented from seeing the other (Opaque condition). Bars represent the mean \pm SEM excess of observed samples with joint writhing above the expected value, as a percentage. ** $P < 0.01$ compared to Control group (Student's t test).



blocked the co-occurrence of writhing behavior in the BW condition (Fig. 2B). Zinc sulfate treatment destroys the olfactory epithelium in the mouse but spares axonal transport from the vomeronasal organ to the accessory olfactory bulb (10), and thus pheromonal communication cannot be ruled out. It is, of course, highly likely that the recognition of the other mouse in the dyad as stranger, familiar, or sibling was achieved via olfactory cues (11), which were likely unimpeded by the barriers. Indeed, social communication is recognized to be commonly multimodal in many species (12).

An existing data set (13) provided an independent verification of the social co-occurrence of pain behavior in simultaneously tested mice, in another assay. In the 5% formalin test, licking behavior was statistically time-synchronized within runs of four mice tested individually in Plexiglas observation cylinders, but in close

proximity and in full view of each other (figs. S6 and S7A). The co-occurrence of pain behaviors in familiar individuals may itself be evidence of empathy, representing a compelling analog to the demonstrations of physiological linkage in empathizing humans (7).

These formalin data also showed a reduction of between-subject variance within a run (fig. S7B), suggesting that subjects' pain behaviors were being influenced, perhaps bidirectionally, by their neighbors. In a new experiment, we compared pain behavior in "both licking" dyads in which both mice received either a high dose (5%) or a low dose of formalin (1%), or in which each mouse received different doses (1%, 5%). Pain behavior was influenced by that of the neighbor mouse, such that licking times were marginally increased in mice receiving the low dose while observing a high dose-injected cagemate, and significantly reduced in mice

receiving the high dose while observing a low dose-injected cagemate (Fig. 3). No significant effects were observed among strangers (fig. S9).

Finally, we investigated whether the observation of a cagemate in pain could modulate sensitivity to pain of a wholly different modality. Mice were tested in dyads as described, but in addition to measuring writhing behavior, we tested all mice for their sensitivity to withdraw from a noxious radiant heat stimulus before and at 5-min intervals after injection of acetic acid (or no injection). Injection and the mere observation of a cagemate's writhing behavior both produced significant and equivalent thermal hyperalgesia (Fig. 4). No observation effects whatsoever were observed among strangers (fig. S10). Concurrent thermal pain testing did not abolish the BW/OW increase in writhing behavior (Fig. 4C), and a significant correlation was observed between the writhing behavior of

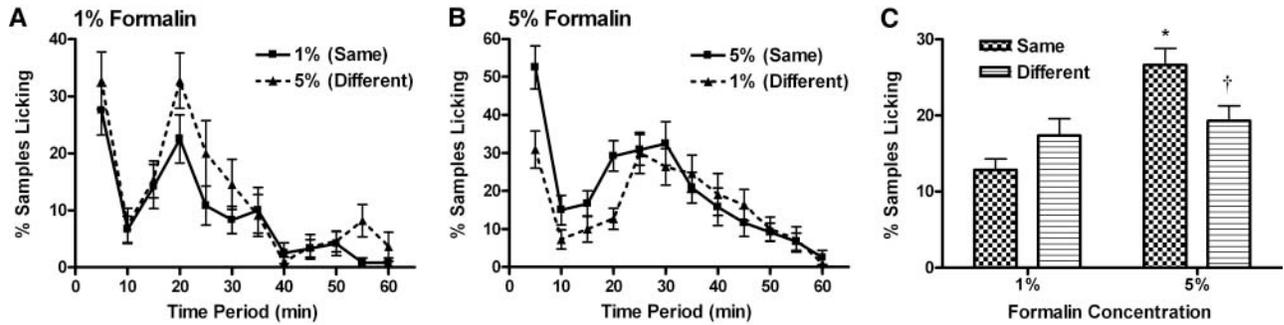


Fig. 3. (A and B) Bidirectional modulation of pain behavior produced by observation of a cagemate in the formalin test. Mice, all nonsibling cagemates ($n = 22$ to 24 per group; housed together for >21 days), were tested in dyads. In the “Same” condition, both mice received either 1% formalin or 5% formalin. In the “Different” condition one mouse received 1% formalin and the other received 5% formalin. All groups displayed the expected biphasic pattern of responding (A and B). A two-way (injected dose \times observed dose) repeated measures analysis of variance (ANOVA) revealed a significant three-way interaction ($P < 0.05$). (A) Data from all mice receiving 1% formalin; the legend describes the status of the other mouse in

the dyad. (B) Data from all mice receiving 5% formalin; the legend describes the status of the other mouse in the dyad. In (A) and (B) (note different ordinate scales), symbols represent the mean \pm SEM percentage of sampled intervals showing formalin-induced recuperative behavior (% Samples Licking) per 5-min time bin. (C) Totals in all conditions from 0 to 40 min after injection, after which there was no longer significantly different licking behavior between 1% and 5% groups. ANOVA revealed a highly significant injected dose \times observed dose interaction ($F_{1,88} = 9.3, P < 0.005$). $*P < 0.05$ compared to analogous 1% condition. $\dagger P < 0.05$ compared to analogous “Same” condition.

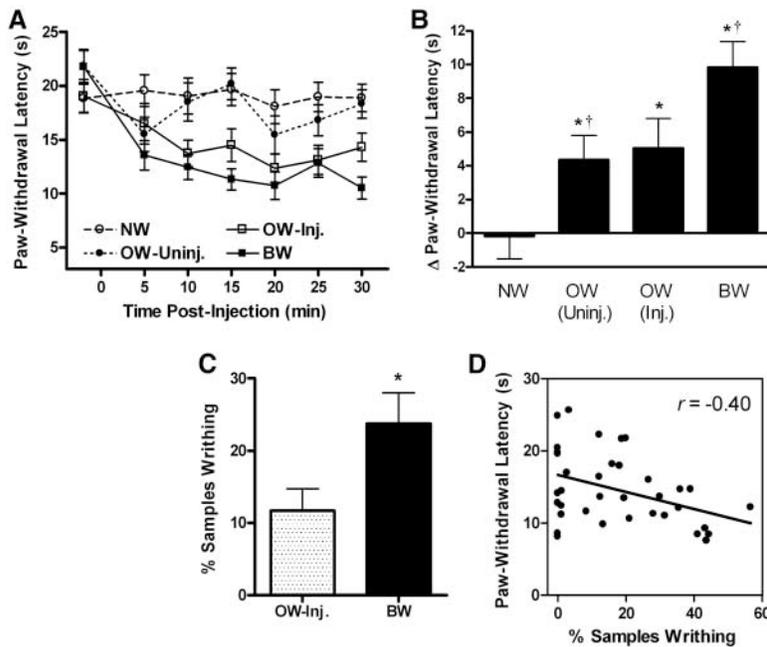


Fig. 4. (A to D) Thermal hyperalgesia produced by injection of acetic acid, by mere observation of a cagemate injected with acetic acid, or both. Mice (all nonsibling cagemates; $n = 28$ to 31 per group; housed together for >21 days) were tested in dyads as described in Fig. 1. Before injection, all mice were tested for baseline thermal sensitivity. In the BW (“both writhing”) group, both mice were removed at time = 0, given an injection of 0.9% acetic acid, and returned to their cylinder. In the NW (“none writhing”) group, both mice were removed and replaced, with neither receiving any injection. In the OW (“one writhing”) group, one mouse received an acetic acid injection (OW-Inj.) and the other (OW-Uninj.) did not. All mice were retested for thermal sensitivity at 5-min intervals for 30 min. Symbols in (A) represent the mean \pm SEM paw-withdrawal latencies (average of both hindpaws). Bars in (B) represent the mean \pm SEM average change in paw-withdrawal latencies from the baseline latency. $*P < 0.05$ compared to NW group and zero; $\dagger P < 0.05$ compared to the group immediately to the left. Bars in (C) represent the mean \pm SEM percentage of sampled intervals showing writhing behavior (% Samples Writhing) of mice receiving acetic acid (both mice in BW group; OW-Inj. mice). $*P < 0.05$ compared to OW-Inj. group. (D) A significant correlation ($r = -0.40; P < 0.05$) between the writhing behavior of one mouse in a dyad (ordinate; BW and OW-Inj. only) and the average (postinjection) paw-withdrawal latency of its dyadic counterpart (abscissa; BW and OW-Uninj. only).

one mouse in the dyad and the thermal hyperalgesia exhibited by the other (Fig. 4D). These data suggest that the pain system is sensitized in a general manner by the observation of pain in a familiar, and furthermore demonstrate that socially mediated hyperalgesia can be elicited in the clear absence of imitation. Mechanisms underlying these phenomena are thus more likely to be found in the sensory/perceptual system than in the motor system.

Rodents are known to recognize and have emotional reactions to the pain of conspecifics (2), and their pain sensitivity can be altered by social factors (14–17). However, most of these studies reported analgesia rather than hyperalgesia and did not evaluate effects in real time, when another’s pain was actually being observed. These phenomena may represent an example of coaction social facilitation, depending on one’s definition of that term (18). However, our findings are consistent with the perception-action model of empathy proposed by Preston and de Waal (1), both in the automatic priming of somatic responses in a state similar to that of the attended object and in the modulating effects of familiarity and similarity of experience between subject and object. Our observations cannot be easily explained by stress, imitation, or conditioning, and they neither depend on nor necessarily indicate the presence of sympathy, conscious (cognitive) representations, or altruism. Empathy for pain is currently a topic of much study in humans (19–21), and “mirror neurons” responding to another’s pain may have been identified in human anterior cingulate cortex (22). A large human literature documents the effects on pain report of observation of pain in others (23); the present data suggest that these effects may be mediated precognitively. There are clear limitations to the mechanistic information that can be gleaned from human

studies; the availability of an animal model of empathy will allow the application of far more powerful experimental techniques.

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25. This work was supported by the Louise Edwards Foundation. We thank E. Balaban, C. Bushnell, and J. Lund for helpful discussions.

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Materials and Methods

SOM Text

Figs. S1 to S10

References

4 April 2006; accepted 26 May 2006

10.1126/science.1128322