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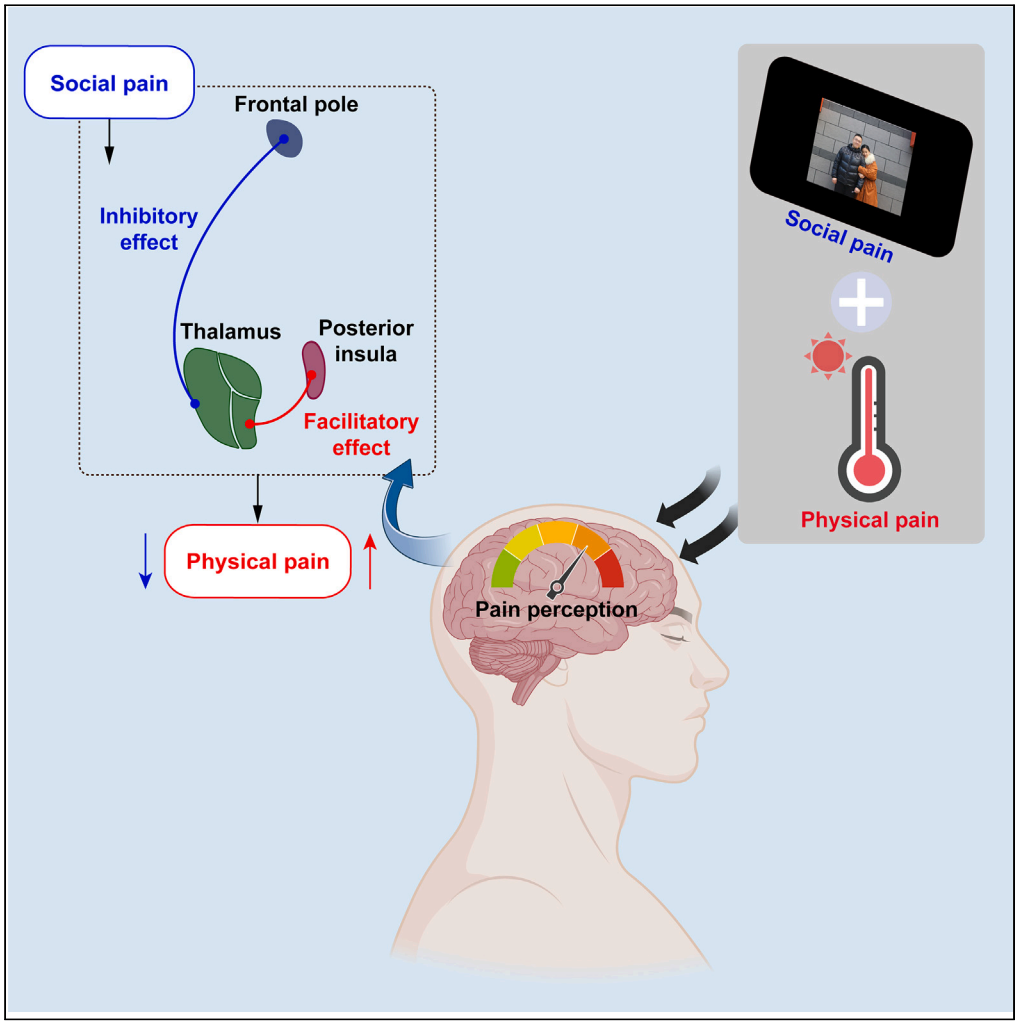


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## Highlights

Social pain facilitates and inhibits physical pain perception

The posterior insula encoded social pain's facilitatory effect on physical pain

The frontal pole encoded social pain's inhibition effect on physical pain

The thalamus modulated and predicted facilitation and inhibition processes

Zhang et al., iScience 27, 108951
February 16, 2024 
https://doi.org/10.1016/j.isci.2024.108951

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# The dual facilitatory and inhibitory effects of social pain on physical pain perception

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## SUMMARY

**Pain is a multi-dimensional phenomenon that encompasses both physical pain experienced physiologically and social pain experienced emotionally. The interactions between them are thought to lead to increased pain load. However, the effect of social pain on physical pain perception during interactions remains unclear. Four experiments were conducted merging physical and social pains to examine the behavioral pattern and neural mechanism of the effect of social pain on physical pain perception. Seemingly paradoxical effects of social pain were observed, which both facilitated and inhibited physical pain perception under different attention orientations. Brain imaging revealed that the posterior insula encoded the facilitatory effect, whereas the frontal pole engaged in the inhibitory effect. At a higher level, the thalamus further modulated both processes, playing a switch-like role under different concern statuses of social pain. These results provide direct evidence for the dual-pathway mechanism of the effect of social pain on physical pain.**

## INTRODUCTION

Pain is a complex phenomenon which can be classified into different types: physical pain, which is associated with actual or potential tissue damage, and social pain, which is related to the experience of psychological distance from other individuals or social groups (e.g., exclusion, rejection).[1] Physical pain, when triggered by a noxious stimulus, is typically short-lived, whereas social pain may persist for a longer period of time.[2] Social pain not only brings about unpleasant experiences, which can include physical pain, but can also affect physical perceptions,[3] seemingly reducing one's tolerance of physical pain and even enhancing pain perception, demonstrating a facilitatory effect.[4] In light of this, the role of social pain in perceiving physical pain cannot be ignored.[5]

Although many studies have focused on comparisons of the similarities and differences between social and physical pain, research on the actual interactions between social and physical pain is quite limited. Many individuals, such as those with mental disorders,[6] cannot avoid experiencing physical and social pain jointly. When this happens, the extent to which social and physical pain exaggerate one another is unclear. Clarifying the potential effects of social pain would be greatly beneficial in terms of exploring effective treatments to alleviate physical pain and further inform our understanding of the interactions between social behavior and pain, particularly in situations where individuals suffer from social pain due to diseases that cause physical pain, for instance, patients with mental disorder, physical disability caused by trauma, and female patients with migraine.[7] Therefore, we attempted to address this gap in understanding by conducting a series of repeatable behavioral and fMRI experiments.

When processing two separate types of stimuli simultaneously, the perception of one stimulus may be influenced by the experiencing of the other.[8] Therefore, in the current study, we manipulated one stimulus—social pain—to target our focus, investigating how social pain affected physical pain perception in various situations. Psychological factors such as attention and cognitive load play vital roles in shaping experiences of both physical and social pain.[9] Pain perception depends on the interaction between peripheral noxious afferents and the processing of stimuli in the central nervous system.[10] Correspondingly, psychological factors can affect this neural processing and trigger modulation effects that can either facilitate or inhibit sensations of pain.[11] Furthermore, specific regions of the brain are crucial in the pain modulation process. For example, the insula has been shown to be involved in the processing of physical and social pain,[12] particularly in constructing pain perception.[13] Meanwhile, the frontal pole is involved in the affective networks within the social-physical pain matrix.[14] Notably, the thalamus is a core relay station for transmitting nociceptive information, and as such, its connections with other regions have been found to be related to pain modulation.[15] These regions may play critical roles in pain perception under different circumstances. However, the various potential effects of social pain on physical pain perception may rely on complex mechanisms, particularly the co-integration of these crucial areas and the functional networks between them.

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https://doi.org/10.1016/j.isci.2024.108951

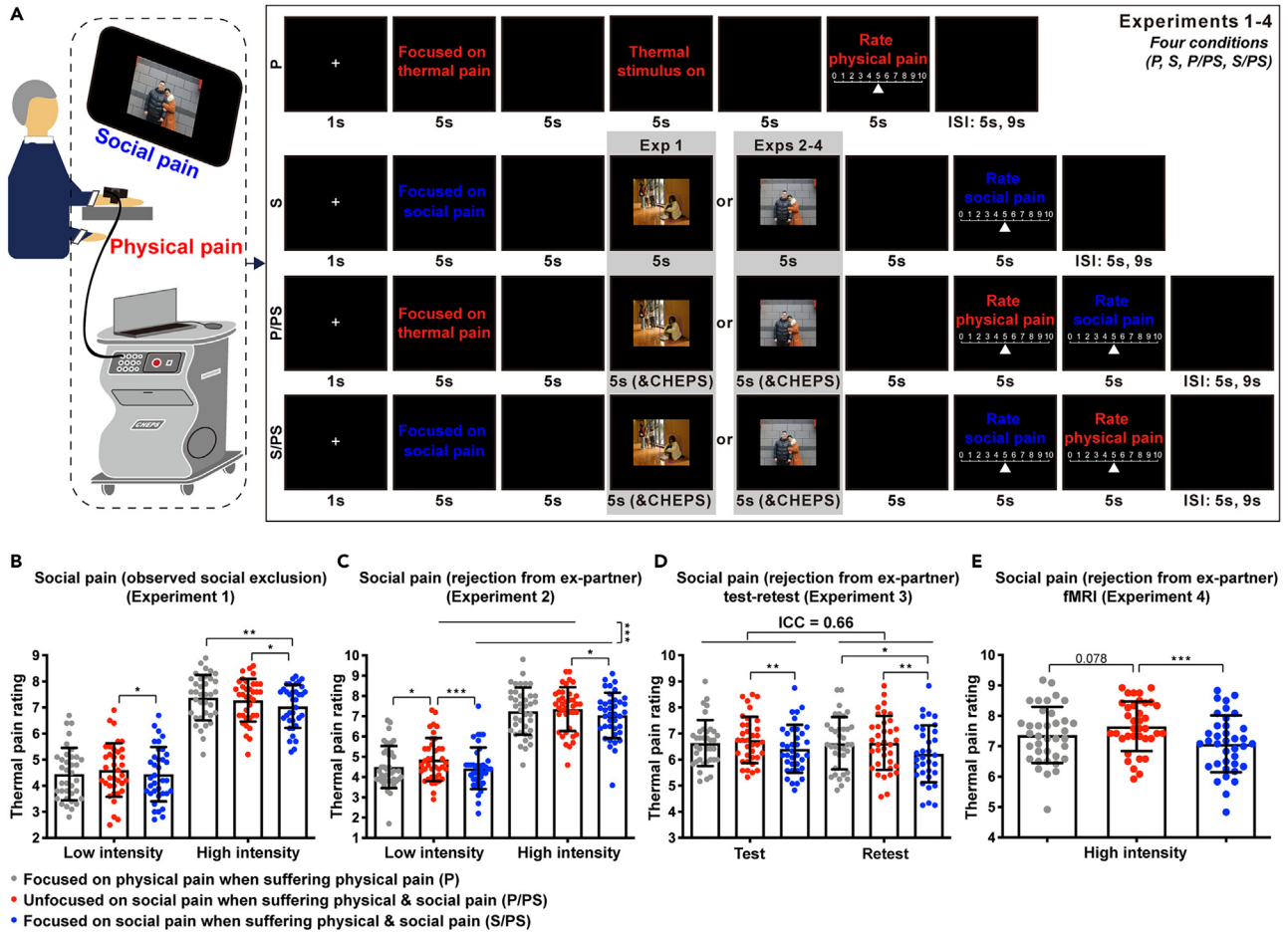


**Figure 1. Overview of experimental setup and behavioral results**

(A) In each experiment, participants rated their perceptions of their suffering in response to the physical pain stimulus (heat-evoked pain), the social pain stimulus (feelings elicited by scenes depicting social exclusion or photographs related to romantic rejection), or both. Experiment 1 included four basic conditions: physical pain (P), social pain based on social exclusion (S), not focusing on social pain while suffering both physical and social pain (P/PS), and focusing on social pain while suffering both physical and social pain (S/PS). Experiments 2 to 4 also had four conditions each, but in these, the social pain was based on romantic rejection.

(B) Effects of social pain based on social exclusion on the perception of physical pain.

(C) Effects of social pain based on romantic rejection.

(D) Reproducibility of the intra-individual effects of social pain.

(E) Effects of social pain on physical pain perception in the fMRI experiment (error bars represent SD, *p < 0.05, **p < 0.01, ***p < 0.001).

Based on the aforementioned considerations, our study first focused on how social pain modulates the perception of physical pain during the interactions between social and physical pain. We were also interested in whether social pain caused by different social situations (i.e., social exclusion or rejection) would have similar effects on pain perception. Given that some brain regions (e.g., insula, thalamus) have been shown to play essential roles in pain modulation, we expected that the potential effects of social pain might depend on distinct brain activities in these pain-related regions. Thus, we were primarily concerned about the underlying brain mechanisms in perceiving physical pain during complex interactions.

## RESULTS

### Inhibitory effect of social exclusion on the perception of physical pain

Experiment 1 examined the effects of social pain on physical pain perception as participants experienced both physical and social pain simultaneously (Figure 1). Using scenarios of social exclusion as experienced on campus to arouse their experience of social pain, participants were instructed as to which type of pain they should focus upon. Three conditions were tested under both low and high thermal pain: (1) the participant focused on physical pain while suffering physical pain alone (P); (2) the participant focused on the physical pain they felt while suffering both physical and social pain (P/PS); and (3) the participant focused on the social pain they felt while suffering both physical and social pain

**Table 1. Demographics and information on social pain for Experiments 1 to 4**

| | Experiment 1 | Experiment 2 | Experiment 3 | Experiment 4 |
|---|---|---|---|---|
| Paradigm | social exclusion | social rejection | social rejection (test-retest) | social rejection (fMRI) |
| Sample size | 36 | 39 | 36 | 37 |
| Sex | | | | |
| Female | 18 | 21 | 18 | 22 |
| Male | 18 | 18 | 18 | 15 |
| Age (years) | 23.81 ± 2.16 | 23.03 ± 2.82 | 23.78 ± 2.84 | 22.95 ± 2.28 |
| Age range (years) | 19–29 | 19–30 | 19–29 | 20–29 |
| Room temperature (°C) | 23.12 ± 1.43 | 22.59 ± 1.74 | 23.03 ± 0.88<br>22.51 ± 0.91 | 19.34 ± 0.78 |
| Arm temperature (°C) | 31.77 ± 0.75 | 31.32 ± 1.03 | 36.31 ± 0.18<br>36.29 ± 0.17 | 36.20 ± 0.64 |
| Pain threshold (°C) | 43.44 ± 0.69 | 42.90 ± 1.99 | 43.56 ± 0.83<br>43.97 ± 1.01 | 42.72 ± 1.09 |
| Thermal stimulus | | | | |
| Low (°C) | 44.28 ± 0.74 | 43.86 ± 1.93 | – | – |
| High (°C) | 45.18 ± 0.75 | 44.83 ± 1.92 | 45.36 ± 0.82<br>45.93 ± 0.98 | 44.69 ± 0.93 |
| Social pain | | | | |
| Rejection | – | 5.23 ± 0.99 | 5.11 ± 1.01 | 5.51 ± 0.80 |
| Love intensity | – | 1.56 ± 0.91 | 1.81 ± 0.95 | 1.84 ± 0.96 |
| Reuniting intention | – | 2.08 ± 0.77 | 2.11 ± 0.75 | 1.84 ± 0.65 |
| Social pain rating | | | | |
| S | 4.51 ± 1.65 | 4.65 ± 1.68 | 4.54 ± 2.07<br>4.03 ± 1.99 | 5.07 ± 1.88 |
| P/PS | 4.53 ± 1.43 | 4.73 ± 1.71 | 4.64 ± 2.10<br>4.13 ± 2.02 | 5.21 ± 1.86 |
| S/PS | 4.67 ± 1.59 | 4.92 ± 1.69 | 4.81 ± 2.20<br>4.37 ± 2.14 | 5.43 ± 1.92 |

**Notes: Rejection** = Mean score of the question: To what extent did you feel rejected by your ex-partner in the breakup experience? (1 = *not at all*, 7 = *extremely*); **Love intensity** = Mean score of the question: Did you still love your ex-partner when you broke up? (1 = *not at all in love*, 2 = *unsure/it's complicated*, 3 = *still in love*); **Reuniting intention =** Mean score of the question: Do you want to get back together with your ex-partner if given the chance? (1 = *no*, 2 = *unsure*, 3 = *yes*).

(S/PS). One further condition was also tested in which participants focused on social pain while suffering from social pain alone (S). Two-way repeated ANOVA using the pain rating of the thermal stimulus as the dependent variable revealed significant main effects of the condition (i.e., P vs. P/PS vs. S/PS), the thermal stimulus intensity (i.e., low vs. high), and the interaction effect of the two on physical pain perception: $F(2,70) = 6.73$, $p = 0.002$, $\eta_p^2 = 0.16$; $F(1,35) = 300.72$, $p < 0.001$, $\eta_p^2 = 0.90$; $F(2,70) = 4.02$, $p = 0.022$, $\eta_p^2 = 0.10$. Post hoc analysis revealed that the pain ratings in the S/PS condition (Mean ± *SD*, 7.04 ± 0.83) were significantly lower than those in the P condition (7.38 ± 0.87) at high intensity, indicating an inhibitory effect: $t(70) = -3.57$, $p = 0.003$, $d = 0.40$, 95% CI = [–0.57, –0.10] (Figure 1B; Table 1). Meanwhile, the pain ratings in the S/PS condition (low: 4.44 ± 1.04; high: 7.04 ± 0.83) were significantly lower than those in the P/PS condition (low: 4.60 ± 1.03; high: 7.28 ± 0.82) at both intensity levels: $t_{low}(70) = -2.78$, $p = 0.026$, $d = 0.15$, 95% CI = [–0.31, –0.02]; $t_{high}(70) = -2.78$, $p = 0.025$, $d = 0.29$, 95% CI = [–0.45, –0.02]. These results indicate an inhibitory effect of social pain on physical pain perception, which is to say that participants reported experiencing lower physical pain when they focused on social pain while experiencing both types of pain at once.

## Facilitatory effect of social rejection on the perception of physical pain

Experiment 2 examined the effect of social pain based on romantic rejection. The recruited participants had recently experienced an unwanted break-up and felt rejected. This romantic rejection was used to induce social pain by showing participants photographs of their ex-partner.[16] The results revealed that the pain ratings in this context varied according to both the condition (i.e., P vs. P/PS vs. S/PS) and the intensity (i.e., low vs. high): $F(2,76) = 6.19$, $p = 0.003$, $\eta_p^2 = 0.14$; $F(1,38) = 280.48$, $p < 0.001$, $\eta_p^2 = 0.88$. The independent *t* test was used to examine the various potential effects on pain intensities. We found that the low-intensity pain ratings in the P/PS condition

(4.87 ± 1.07) were higher than those in the P condition (4.50 ± 1.04), showing a facilitatory effect: $t(76) = 2.48$, p = 0.053, $d = 0.35$, 95% CI = [–0.00, 0.75]. Meanwhile, the pain ratings at both intensity levels in the S/PS condition (low: 4.43 ± 1.03; high: 7.05 ± 1.12) were significantly lower than those in the P/PS condition (low: 4.87 ± 1.07; high: 7.36 ± 1.08), suggesting a potential inhibitory effect: $t_{low}(76) = -4.38$, p < 0.001, $d = 0.42$, 95% CI = [–0.69, –0.19]; $t_{high}(76) = -2.98$, p = 0.015, $d = 0.28$, 95% CI = [–0.57, –0.05] (Figure 1C).

These results suggest that social pain can induce both inhibitory and facilitatory effects, which is to say that individuals reported lower physical pain when they were focused on social pain, and higher physical pain when they did not focus on social pain.

## Reproducibility of intra-individual effects

The results from Experiments 1 and 2 revealed the general effects of social pain across various paradigms and samples. Therefore, Experiment 3 examined these effects further to determine whether they were stable, and could be reproduced across time periods. To do this, participants completed the same tasks a second time at a follow-up session which took place 7 to 14 days after the initial session. Two-way ANOVA revealed a main effect of the condition (i.e., P vs. P/PS vs. S/PS) on physical pain perception: $F(2,34) = 10.83$, p < 0.001, $\eta_p^2 = 0.39$ (Figure 1D). The pain ratings in the S/PS condition (6.32 ± 1.00) were significantly lower than those in either the P condition (6.63 ± 0.94) or the P/PS condition (6.70 ± 0.96) in both follow-up tests: $t(34) = -2.95$, p = 0.016, $d = 0.32$, 95% CI = [–0.57, –0.05]; $t(34) = -4.70$, p < 0.001, $d = 0.39$, 95% CI = [–0.58, –0.17]. The main effect of test order (i.e., test vs. retest) and the interaction were insignificant: $F(1,35) = 0.71$, p = 0.406; $F(2,70) = 1.22$, p = 0.30. We also calculated the intra-class correlation coefficient (ICC) for the average ratings of physical and social pain separately ($ICC_{physical\ pain\_mean} = 0.66$; $ICC_{social\ pain\_mean} = 0.92$), as well as the pain ratings for each condition on its own ($ICC_P = 0.65$; $ICC_{P/PS} = 0.68$; $ICC_{S/PS} = 0.54$) to examine the consistency of the test and retest results. The retest results duplicated the effects of social pain, indicating good reliability of individual reproducibility.

Similarly, the behavioral results of the fMRI experiment generally repeated the effects observed in Experiments 1 and 2, in that the pain ratings varied according to condition (i.e., P vs. P/PS vs. S/PS): $F(2,72) = 8.99$, p < 0.001, $\eta_p^2 = 0.20$. The pain ratings in the S/PS condition (7.08 ± 0.93) were significantly lower than in the P/PS condition (7.66 ± 0.82), suggesting a potential inhibitory effect: $t(35) = -5.86$, p < 0.001, $d = 0.66$, 95% CI = [–0.83, –0.33] (Figure 1E). Moreover, the pain ratings in the P/PS condition (7.66 ± 0.82) were marginally significantly higher than those in the P condition (7.37 ± 0.92), suggesting a potential facilitatory effect: $t(35) = 2.32$, p = 0.078, $d = 0.33$, 95% CI = [–0.02, 0.60].

## Brain activity related to the facilitatory or inhibitory effect

In Experiment 4, we explored the underlying brain mechanisms engaged in the facilitatory or inhibitory effect. We first examined pain-related brain activity in different contrasts using whole-brain analysis (see supplemental information, Figure S1). Increased activity was observed in the posterior insular cortex [40, –3, 6], frontal pole [40, 44, 26], thalamus [–10, –24, 6], anterior cingulate cortex [–5, –3, 41], and posterior cingulate cortex [11, –27, 41] in the P condition when contrasted against the S condition (Figure 2A). Increased activity was also seen in the anterior insular cortex [–31, 14, –15], frontal pole [4, 63, –1], thalamus [17, –32, 4], anterior cingulate cortex [–2, 35, –4], posterior cingulate cortex [1, –46, 23], orbitofrontal cortex [–44, 29, –11], amygdala [22, –6, –14], and hippocampal gyrus [31, –21, –15] in the S condition when contrasted against the P condition. These increased brain activities indicated that both social and physical pain elicit a general effect on brain activation. Meanwhile, activity in most regions was also observed in the additional results of the conjunction analysis (Figure S2). Importantly, our analysis revealed increased activity in both the insular cortex ([–31, 11, –16], [40, –1, –1]) and the frontal pole ([2, 58, –8], [40, 46, –2]) in the contrasts of P < P/PS (i.e., a facilitatory effect) and S/PS < P (i.e., an inhibitory effect; Figure 2B). These findings suggest that both the insula and the frontal pole may play important roles in the facilitation and inhibition processes of physical pain perception.

We further extracted the differences in activity observed in these key regions (i.e., the insular cortex and the frontal pole) in the effect-related contrasts to explore the brain activity involved in the facilitatory and inhibitory effects. The changed activity of the posterior insula in the contrast of S < P was negatively correlated with that of the frontal pole in the contrast of P < S ($r = -0.36$, p = 0.026; Figure 2D). Moreover, the changed activity of the posterior insula in the contrast of S/PS < P was positively correlated with the differences in reported pain ratings between the S/PS condition and the P condition ($r_{posterior\ insula} = 0.36$, p = 0.028; Figure 2C). In contrast, the changed activity in the frontal pole in the contrast of S < P was negatively correlated with the pain ratings reported in the S/PS condition ($r_{frontal\ pole} = -0.33$, p = 0.047; Figure 2E). These correlations between brain activity and physical pain perception demonstrate that facilitatory and inhibitory processes (i.e., positive correlation suggesting a facilitatory effect, and negative correlation suggesting an inhibitory effect) might occur in the insular cortex and the frontal pole, respectively.

## Encoding mechanism involved in the facilitatory and inhibitory processes

The general linear model (GLM) with the facilitatory-related or inhibitory-related effect as a regressor of interest was used to determine the activation of the facilitation or inhibition processes. We found that pain ratings positively correlated with brain activation in the posterior insula ([43, –7, 0]) in the P/PS condition ($r = 0.70$, p < 0.001; Figure 3A). More importantly, the difference between reported pain ratings in the P/PS condition and in the P condition (i.e., the facilitatory effect) was also positively correlated with the change in activity in the posterior insula ([39, –16, 6]) in the contrast of P < P/PS ($r = 0.50$, p = 0.0015; Figure 3B). Furthermore, the model using brain activation in the posterior insula as mediator was significant: $R^2 = 0.29$, $MSE = 0.42$, $F(2,34) = 7.10$, p = 0.0027. A marginally significant indirect effect was found via activation in the posterior insula ($b = 0.0698$, $SE = 0.0384$, 95% CI = [0.0160, 0.1663]; Figure 3C), implying that the insula plays an essential role in the facilitatory effect.

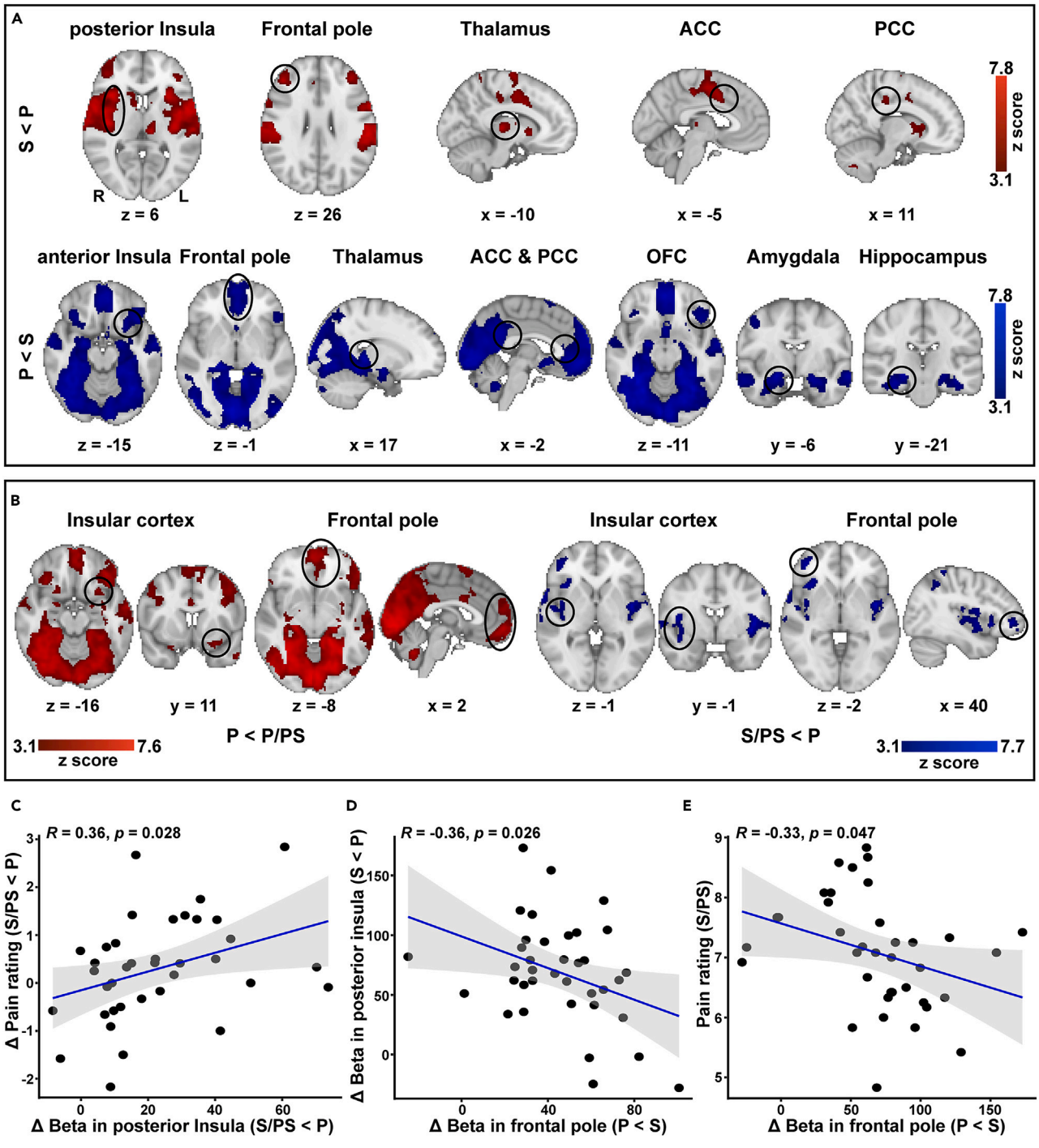


**Figure 2. Brain activity related to the facilitatory and inhibitory effects**

(A) Brain activation in the P condition as compared to the S condition (top), and in the S condition as compared to the P condition (bottom).

(B) Brain activation in the P/PS condition as compared to the P condition (left), and in the P condition as compared to the S/PS condition (right; $p < 0.05$; cluster-corrected 3.1).

(C) The posterior insula showed a positive correlation between the changed BOLD response magnitude and the difference in pain perception in the contrast of S/PS < P.

(D) Brain activity in the posterior insula was negatively correlated with that in the frontal pole.

(E) The frontal pole showed a negative correlation between the changed BOLD response magnitude in the contrast of P < S and the pain ratings in the S/PS condition.

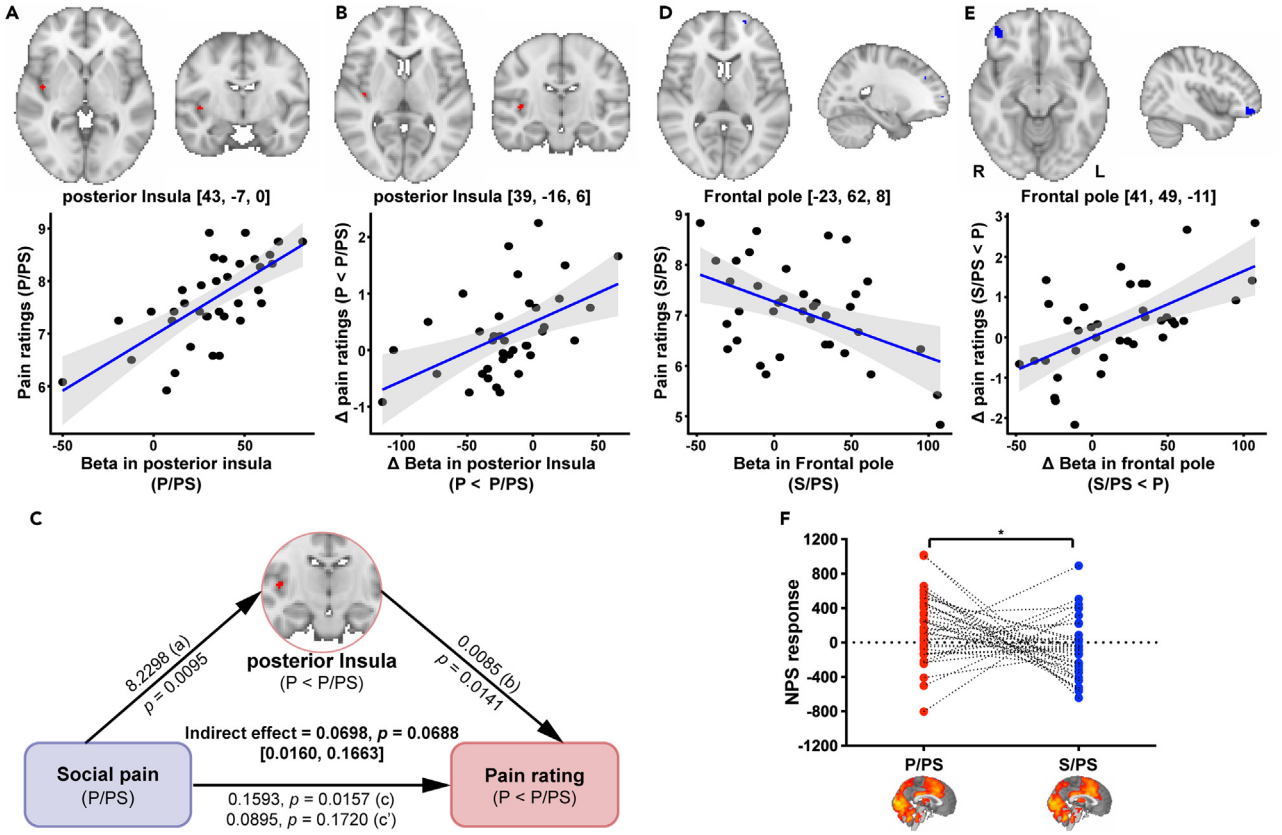


**Figure 3. Encoding activities involved in the facilitatory or inhibitory effect**

(A) The posterior insula showed a positive correlation between the BOLD response magnitude and the pain ratings in the P/PS condition.

(B) The posterior insula showed a positive correlation between the changed BOLD response magnitude and the facilitatory effect (i.e., the difference in the pain ratings) in the contrast of P < P/PS.

(C) Activity in the posterior insula mediated how social pain (i.e., the ratings of social pain in the P/PS condition) affected physical pain perception.

(D) The frontal pole showed a negative correlation between the BOLD response magnitude and the pain ratings in the S/PS condition.

(E) The frontal pole showed a positive correlation between the changed BOLD response magnitude and the inhibitory effect (i.e., the difference in the pain ratings) in the contrast of S/PS < P.

(F) NPS responses in the contrasts of P < P/PS and S/PS < P (*p < 0.05).

The pain ratings in the S/PS condition were found to be negatively correlated with the brain activity in the frontal pole [–23, 62, 8]) in the S/PS condition ($r = -0.47$, p = 0.0034; Figure 3D). This negative correlation indicates an inhibitory effect from the frontal pole. Moreover, the difference in pain ratings in the P condition as compared to the S/PS condition (i.e., inhibitory effect) positively correlated with the changed activity in the frontal pole ([41, 49, −11]) in the contrast of S/PS < P ($r = 0.61$, p < 0.001; Figure 3E), suggesting a demonstrable role of the frontal pole in the inhibition effect.

## Thalamus modulated the facilitation and inhibition processes

To characterize the spatial network patterns associated with the facilitation process, we performed a psychophysiological interaction (PPI) analysis for the P/PS condition using the posterior insula as the seed. This revealed significantly increased functional connectivity between the posterior insula and the thalamus ([5, −10, 10]; Figure 4A), which positively correlates with the facilitatory effect (i.e., the difference in pain ratings in the P/PS condition as compared to the P condition: $r = 0.72$, p < 0.001; Figure 4D). Moreover, the results of the model that used insula-thalamus connectivity as the mediator were significant: $R^2 = 0.59$, $MSE = 0.24$, $F(2,34) = 21.88$, p < 0.001. A significant indirect effect was found via insula-thalamus connectivity ($b = 0.0045$, $SE = 0.0022$, 95% CI = [0.0009, 0.0088]; Figure 4J) which predicted pain perception under the facilitatory effect. More interestingly, the serial mediation model using the posterior insula as Mediator 1 and the insula-thalamus connectivity as Mediator 2 also reached significance: $R^2 = 0.62$, $MSE = 0.23$, $F(3,33) = 17.08$, p < 0.001. This reveals a significant indirect effect of social pain on pain perception via the path from the posterior insula to the insula-thalamus connectivity (i.e., social pain → insula → insula-thalamus connectivity → pain rating; $b = 0.0339$, $SE = 0.0204$, 95% CI = [0.0055, 0.0897]; Figure 4K). Thus, insula-thalamus connectivity appears to mediate how the posterior insula affects physical pain perception. These findings reveal the modulation of the thalamus in the facilitatory process.

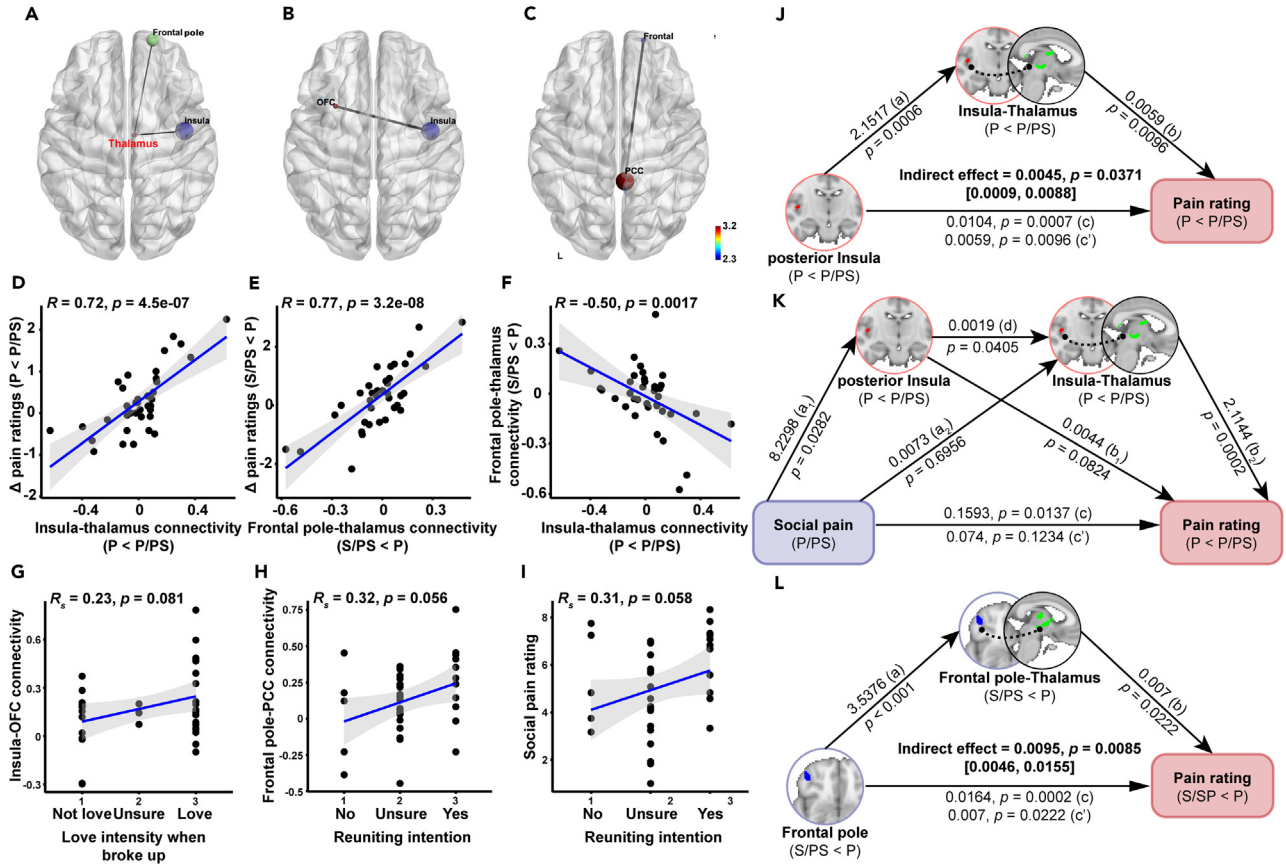


**Figure 4. The thalamus modulated the facilitation and inhibition processes**

(A) PPI analysis of the P/PS and S/PS conditions revealed increased functional connectivity between the thalamus and seeds (i.e., the insula or the frontal pole; node sizes indicate T-value, edge sizes indicate connectivity strength, cluster-corrected 2.3, p < 0.05).

(B) PPI analysis of the P/PS condition suggested ex-partner-related insula-OFC connectivity.

(C) PPI analysis of the S/PS condition revealed ex-partner-related frontal pole-PCC connectivity.

(D) Correlation between insula-thalamus connectivity and difference in pain ratings in the P/PS condition compared to the P condition.

(E) Correlation between frontal pole-thalamus connectivity and difference in pain ratings in the P condition compared to the S/PS condition.

(F) Correlation between insula-thalamus connectivity and frontal pole-thalamus connectivity.

(G) Correlation between insula-OFC connectivity and love intensity when the relationship ended.

(H) Correlation between frontal pole-PCC connectivity and reuniting intention.

(I) Correlation between reuniting intention and social pain.

(J) Insula-thalamus connectivity mediated how brain activity in the posterior insula affected physical pain perception.

(K) Posterior insula and insula-thalamus connectivity mediated how social pain affected physical pain perception.

(L) Frontal pole-thalamus connectivity mediated how brain activity in the frontal pole affected physical pain perception.

Another PPI analysis was then conducted using the frontal pole as the seed for the S/PS condition to examine the mechanism of the inhibition process. The results revealed increased functional connectivity between the frontal pole and the thalamus ([5, −10, 10]; Figure 4A), which positively correlates with the inhibitory effect (i.e., the difference in the pain ratings in the P condition as compared to those in the S/PS condition; $r = 0.77$, $p < 0.001$; Figure 4E). The model using frontal pole-thalamus connectivity as a mediator was significant: $R^2 = 0.63$, $MSE = 0.45$, $F(2,34) = 34.80$, $p < 0.001$. These results reveal a significant indirect effect via frontal pole-thalamus connectivity ($b = 0.0095$, $SE = 0.0036$, 95% CI = [0.0046, 0.0155]; Figure 4L), which predicts physical pain perception under the inhibitory effect. Frontal pole-thalamus connectivity was thus shown to mediate how the frontal pole affects physical pain perception. Our findings also reveal the modulation of the thalamus in the inhibitory process.

Interestingly, insula-thalamus connectivity was negatively correlated with frontal pole-thalamus connectivity ($r = -0.50$, $p = 0.0017$; Figure 4F), suggesting a switch-like role of the thalamus under different concern statuses of social pain. These results indicate that the thalamus plays a crucial regulatory role in both the facilitatory effect (centered by the insula) and the inhibitory effect (centered by the frontal pole) of social pain on overall pain perception.

Furthermore, we also found increased functional connectivity between the posterior insula and the orbitofrontal cortex in the P/PS condition (OFC; [–29, 12, −19]; Figure 4B) and increased functional connectivity between the frontal pole and the posterior cingulate cortex in the S/PS condition (PCC; [5, −45, 35]; Figure 4C). Notably, insula-OFC connectivity was marginally positively correlated with love intensity when breaking up (Spearman's one-tailed $r = 0.23$, $p = 0.081$; Figure 4G), whereas frontal pole-PCC connectivity was marginally positively correlated with reuniting intention (Spearman's $r = 0.32$, $p = 0.056$; Figure 4H). Love intensity when breaking up positively correlated with reuniting intention (Spearman's $r = 0.33$, $p = 0.049$), and reuniting intention marginally positively correlated with social pain (Spearman's $r = 0.31$, $p = 0.058$; Figure 4I). The OFC and PCC are known to be related to the experiencing of both current romantic relationships and social pain,[17] and our results indicate that past romantic experiences also appear to be linked to these regions. These results suggest that the stronger the breakup experience, the stronger the potential connectivity between the physical and social pain regions.

Finally, given the complicated nature of pain perception, we also calculated participants' responses to perceived pain according to the neurological pain signature (NPS) as a superficial verification of whether overall activity in other pain-related regions was consistent with behavioral performance. As expected, the NPS was expressed strongly in the contrast of P < P/PS (Mean ± *SE*, 180.09 ± 64.32) in comparison to the contrast of S/PS < P (−84.81 ± 56.18, $t(36) = 2.44$, $p = 0.02$, $d = 0.72$, 95% CI = [44.62, 485.18]; Figure 3F). Stronger NPS responses were noted in the facilitation process than in the inhibition process, confirming similar patterns in neural activity to those reported at the behavioral level.

## DISCUSSION

To our knowledge, this is the first study to reveal the paradoxical impact of social pain on physical pain, exhibiting both inhibitory and facilitatory effects, and therefore also the first to explore the relevant neural mechanisms involved in this relationship. By eliciting social pain under several different conditions, we observed that: (1) social exclusion inhibited physical pain perception when individuals focused on their social pain; (2) social rejection due to one's romantic partner facilitated physical pain perception when individuals were not focused on their social pain, and inhibited physical pain perception when individuals were focused on their social pain; and (3) these effects were stable over time, demonstrating individual reproducibility. Most importantly, imaging analysis further revealed a dual pathway mechanism: (4) the posterior insula encodes the facilitatory effect, whereas the frontal pole engages in the inhibitory effect. Notably, (5) the thalamus modulates both the facilitation and inhibition processes, further predicting the facilitatory and inhibitory effects by connection couplings. Our study provides direct evidence regarding the effects of processing noxious stimuli under immediate social pain, which provides valuable insights into understanding the complex relationship between social and physical pain. These findings implied that strategies to cope with noxious stimuli are productive components of pain management interventions, particularly for those patients who suffered social pain due to their disease (e.g., mental disorders, physical disability).

### Inhibitory and facilitatory effects of social pain on physical pain

Previous studies have shown that one experiences an increase in physical pain perception after experiencing social pain.[18,19] Consistent with these findings, we also found that social pain had a facilitatory effect when individuals suffer jointly from both physical and social pain. Photographs of ex-partners can be used to arouse negative emotions in individuals due to their past experiences of feeling hurt.[16] Meanwhile, negative stimuli have been shown to further strengthen painful feelings, reflecting the overlap of the impacts of social and physical pain.[19] In the current study, when participants focused on their perceived physical pain, the ignored social pain may have nevertheless been modulating the sensory and affective aspects of the thermal pain,[20] further exacerbating participants' pain perception. However, a stable inhibitory effect was also observed when participants focused on their social pain. Rejection by one's ex-partner, as another form of social pain, appeared to inhibit participants' perception of physical pain, similar to the effect of conditioned pain modulation; that is, pain inhibits pain.[21] Focused social pain could therefore modulate the perception and cognition of nociceptive stimuli by allocating processing resources to relevant stimuli.[22] More specifically, romantic rejection, which often includes feeling a sense of devalued attribution, appears to occupy the process advantage. Accordingly, individuals may be more likely to feel numbness toward physical pain when simultaneously experiencing social pain.

To summarize, our findings show that the effect of social pain on physical pain perception can be either inhibitory or facilitatory. Focusing on social pain can suppress one's perception of physical pain; however, when one does not focus on social pain, pain perception will be exacerbated, implying a triggering role of social pain in pain modulation. These contradictory effects evidenced through our findings point to the importance of considering one's present context and focus, and understanding their potential impacts on one's perception of pain.

### Posterior insula encodes the facilitatory effect

When examining the brain's pain matrix when processing social and physical pain, we found numerous common active regions (e.g., ACC, PCC). However, when considering behavioral relevance, the posterior insula appeared to play the most crucial role in the facilitatory process. The insula is essential in the neural networks engaged in both physical and social pain, and its anterior and posterior parts are known to modulate different aspects of pain.[23] Generally, the anterior insula codes cognition and emotion-related modulation,[24] whereas the posterior insula engages in somatosensory processing and encodes negative emotions.[25,26] In our study, triggering thoughts of romantic rejection was seen to activate the anterior insula (Figure 2A) as well as the posterior insula (Figure 3C) while participants were perceiving physical pain. As an additional noxious stimulus, unfocused social pain becomes superimposed over noxious physical pain, promoting activity in the insula. The increased perception of the physical stimuli thus produces a facilitatory effect, reflecting that pain aggravates pain. Moreover, the

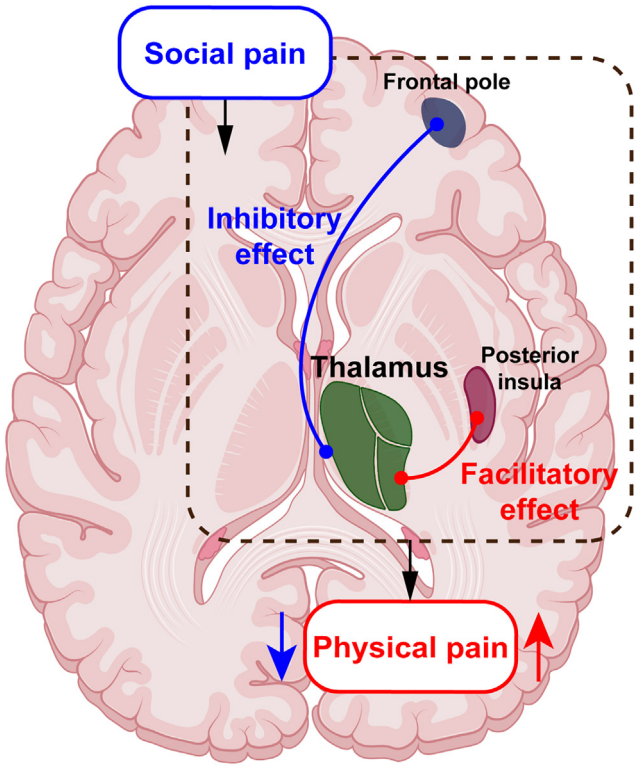


**Figure 5. The model of the thalamus-switch-like pathways**

The model includes the posterior insula-thalamus neural circuit encoding the facilitatory effect, and the frontal pole-thalamus neural circuit engaged in the inhibitory effect (created with BioRender.com).

increased functional connection from the posterior insula to the OFC (related to romantic rejection)[27] may allow the posterior insula to integrate social pain-related information and further modulate physical pain perception. Consequently, the posterior insula can be understood as being a core region involved in the mechanism by which social pain exacerbates physical pain.

## Frontal pole engages in the inhibitory effect

In contrast to our findings regarding the role of the posterior insula in the facilitatory effect of social pain on physical pain perception, the frontal pole was found to be engaged in physical pain perception by way of the inhibition process. The frontal pole is one of the affective networks that form the social-physical pain matrix and is involved in the monitoring or evaluating of decisions at a higher cognitive level.[28,29] When social pain is the primary nociceptive stimulus, it tends to draw and occupy cognitive resources that promote activity in the frontal pole,[30] highlighting and intensifying those feelings of social pain. This therefore weakens the perception of physical pain, resulting in an inhibitory effect. Meanwhile, the increased functional connection from the frontal pole to the PCC (related to rejection sensitivity)[31] can allow the frontal pole to integrate social pain-related information and further reassess other types of painful feelings currently being experienced. Thus, the frontal pole is a crucial region in the perception and processing of social pain which, in this case, can also weaken one's perception of physical pain.

## Thalamus modulates the facilitation and inhibition processes

Although the posterior insula and the frontal pole were seen to play distinct facilitatory and inhibitory roles in our study, we also observed increased pain-related functional connectivity between these two areas and the thalamus. The thalamus serves as an essential component of the modulatory system at the cortex level.[32] It not only constructs pain perception but also controls the key to pain consciousness.[33] As the higher-level center of pain regulation, the thalamus modulates the roles of both the insula and the frontal pole in their facilitatory and inhibitory processes, and can also predict their effects. Cortico-cortical and cortico-subcortical interactions have been shown to modulate nociception.[34] The cortex-cortex interaction observed in our study indicates that social pain-dependent modulation may rely on a mechanism shared with top-down pain modulation. As such, the facilitatory or inhibitory effects of social pain may occur due to increased activity in this core region, which encodes physical pain and induces cortex-cortex interactions to further modify the perception of that physical pain.

Based on our findings, we propose a possible model of "thalamus-switch-like" pathways (Figure 5). The posterior insula and the frontal pole modulate emotional and physical nociceptive inputs, which then trigger the facilitation and inhibition processes separately. Whether one is or is not focused on their experience of social pain, we speculate that the thalamus, at a higher level, modulates pain information

through the initial integration of either the insula or the frontal pole, which will ultimately lead to integrated pain perception. That is, when one focuses on social pain, the posterior insula → thalamus neural circuit is engaged in the facilitatory process; conversely, the frontal pole → thalamus neural circuit is engaged in the inhibitory process. In this model, social pain yields increased functional couplings between key brain regions related to pain processing, further modulating immediate pain perception.

In conclusion, through a series of four experiments, the seemingly paradoxical effects of social pain on the perception of physical pain were observed, revealing a dual pathway mechanism at work when experiencing social and physical pain simultaneously. Specifically, our awareness of experiencing social pain may elicit various effects on the perception of physical pain. These effects occur in specific but distinct brain regions along crucial neural circuits. The dual pathways are centered around the posterior insula and frontal pole, and are modulated by the thalamus at a higher level. Our findings represent a clear departure from the current understanding of the effects of social pain, and provide a new theoretical contribution to our understanding of pain perception. Moreover, our results also suggest the possibility of psychological regulation as a means of moderating the perceptual processing of noxious stimuli, which would be beneficial for human mental health and well-being.

### Limitations of study

The results of this research provide experimental evidence regarding the effects of social pain on physical pain perception during interactions between social and physical pain. However, this study nonetheless has limitations. Even though the facilitatory effect was evident, the facilitatory effect was not significantly stable across the various paradigms, particularly when the pain was at a low intensity. Noxious stimuli with high intensity have been shown to occupy more resources,[31] and this could therefore influence and weaken the facilitation process subtly triggered by social pain. Further systematic studies are necessary to gain a more comprehensive understanding of these processes.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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## SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.108951.

## ACKNOWLEDGMENTS

The authors thank Professor Katja Wiech at the University of Oxford for suggestions on the experimental design. The authors thank Yini Zhang at the University College London, Yunshu Chen at the University of Sydney, and Yupu Zhu at the Institute of Psychology CAS for their help with data collection. This research was supported by the National Natural Science Foundation of China (32100861, 81871436, 32071016, and 82030121) and the National Key R&D Program of China (2022YFC3601701).

## AUTHOR CONTRIBUTIONS

Conceptualization: M.Z. and Y.K.; formal analysis, M.Z. and Y.K.; investigation, X.L., Y.Z., and M.Z.; writing – original draft, M.Z.; writing – review & editing, Y.M. and Y.K.; funding acquisition, M.Z., Y.M., and Y.K.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: November 16, 2023
Revised: December 19, 2023
Accepted: January 15, 2024
Published: January 18, 2024

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## STAR★METHODS

### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| Software and algorithms | | |
| FSL (Version 6.0) | Analysis Group FMRIB of the University of Oxford | https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL |
| SPSS (Version 23) | IBM | https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-23 |
| R (Version 4.2.1) | The R Project for Statistical Computing | https://www.r-project.org |
| Codes and data for fMRI analysis | This paper | https://osf.io/bv9xc/?view_only=6114ecf9e1704cd1bf680111f1d28af9 |
| Other | | |
| An open-access image database of social inclusion/exclusion in young Asian adults (ISIEA) | Zheng et al.[35] | https://link.springer.com/article/10.3758/s13428-021-01736-w |

### RESOURCE AVAILABILITY

#### Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Yazhuo Kong (kongyz@psych.ac.cn).

#### Materials availability

- Social pain stimuli in Experiment 1 are listed in the key resources table.
- There are restrictions to the availability of social pain stimuli in Experiments 2–4 due to participant privacy.

#### Data and code availability

- Behavioral data and the processed fMRI data are listed in the key resources table.
- The source codes for processing the fMRI data are listed in the key resources table.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

### EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

A total of 182 Chinese participants participated in this study (see Table 1). This sample size was deemed sufficient for each experiment to detect a moderate effect according to a power analysis ($f = 0.25$, power = 0.80). All procedures performed in the four studies were in accordance with the ethical standards of the Institutional Review Board of the Institute of Psychology at the Chinese Academy of Sciences (No. H21027) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participants provided their informed consent prior to beginning the experiments, and were debriefed and compensated for their participation after completing all tasks.

### METHOD DETAILS

#### Experiment 1 – Effects of social pain based on social exclusion

##### *Social pain stimuli*

Using scenarios of social exclusion in a university campus setting to arouse feelings of social pain in participants, Experiment 1 examined the effects of social pain on physical pain perception when both types of pain were experienced. Pictures were selected from an open-access image database of social inclusion/exclusion in young Asian adults (ISIEA),[35] and each was assessed in terms of its effectiveness in arousing participants' feelings of social exclusion (Figure 1A). A total of 80 pictures were used, with 60 depicting scenes of social exclusion and 20 depicting neutral social scenes. A total of 34 participants (17 females, age = 24.09 ± 3.17 years, range = 18–30) who did not participate in the main experiment assessed these materials in the pre-experiment. Each picture was rated using three questions: (1) *If you were a part of the scene shown in the picture, would you feel excluded by the others?* (Two options: *yes* or *no*); (2) *If you were a part of the scene shown in the picture, to what extent would you feel excluded by the others?* (response by rating conveyed by a slider from 0 to 100% in increments of 20%; same for the following item); (3) *If you were a part of the scene shown in the picture, to what extent does the scene in the picture feel pleasant or unpleasant?* Pictures that received a "Yes" response to Question 1 from more than 85% of participants were kept. These pictures

were then chosen according to the overall rating they received in Question 2, and the top 30 pictures depicting scenes of social exclusion were selected for use as the visual stimuli for our experiment (exclusion: 65.94 ± 9.24, unpleasant: 68.75 ± 8.96). Then, each image was cropped to a uniform size (800 × 664 pixels), and presented on a screen at a visual angle of 18.92 ° × 12.67 ° during the experiment.

### *Physical pain stimuli*

The thermal stimuli used in all four experiments were produced using a Medoc 9 $cm^2$ contact heat-evoked potential stimulator (CHEPS; Medoc Ltd, Ramat Yishai, Israel). Participants' pain threshold of the thermal stimuli was assessed on their right forearm, 12cm above their wrist, at a 5s inter-stimulus interval using a temperature increase of 40 °C/s. Participants reported the pain they experienced from the brief thermal stimuli using a numerical pain rating scale that ranged from 0 to 10, where 0 = *no feeling*, 1 = *a feeling of warmth*, 2 = *a feeling of heat*, 3 = *a feeling of hotness*, 4 = *beginning to feel painful*, and gradual increases up to 10 = *as painful as could be*.[32] They were also asked to consider the image they had just experienced and to rate the social pain they felt according to the numerical pain rating scale ranging from 0 to 10 (0 = *no feeling*, 1 = *a little uncomfortable feeling*, 2 = *a moderate discomfort feeling*, 3 = *a very uncomfortable feeling*, 4 = *the start of a feeling of heartbroken or suffering* (i.e., the threshold of social pain), with gradual increases until 10 = *a feeling of painful or suffering as bad as it could be*). Specifically, the values from 4 to 10 increased gradually with regards to the degree of pain experienced.[32,36] The mean temperature at which the participant consistently reported they first began to feel pain (i.e., three separate times) was used as the threshold temperature. The pain threshold was used to define the participant's low (i.e., threshold temperature plus 1°C) and high (i.e., threshold temperature plus 2°C) intensities of the thermal stimuli.[32]

### *Procedure*

During the experiment, participants responded to and rated their perception of the thermal and visual stimuli. The experiment consisted of 70 trials, incorporating only thermal, only visual, or a combination of both visual and thermal stimulation. The four conditions (i.e., P, S, P/PS, and S/PS) were intermixed randomly across the three stimuli settings. The presentation of stimuli and manual response measurements were controlled using E-Prime 2.0 (Psychological Software Tools, Inc., Pittsburgh, PA, USA). In each trial, a white fixation cross was first shown on the screen for 1s. Then, one of two instructional phrases was shown for 5s (i.e., the participant was asked to focus only on either the visual or the thermal stimulus; Figure 1A). That is, "*Please perceive the following thermal stimulation carefully, and then you will be asked to rate the pain elicited by the thermal stimulation*" for the P and P/PS conditions, "*Please perceive the following picture carefully. Please try your best to imagine the people in the picture circle as yourself and experience the feelings the pictures' content brings you. Then, you will be asked to rate the painful feelings, heartache, and suffering caused by the scenario" in Experiment 1, and "Please perceive the following picture carefully. Then, you will be asked to rate the painful feelings, heartache, and suffering caused by the photograph*" for the S and S/PS conditions. After that, a black background screen was presented for 5s before a thermal pulse (either low or high intensity) was delivered to the right forearm for 5s with or without an accompanying social exclusion image shown on the screen, or a social exclusion image was displayed on the screen without delivery of a thermal pulse. Then, a black background screen appeared for 5s. The next screen asked participants to consider the sensation of the thermal pulse and/or the image they had just seen, and to rate the physical and/or social pain they felt according to the numerical pain rating scale using their left hand on the response box provided; these instructions were displayed onscreen for 5s. Finally, a black background screen appeared for 5s (or 9s in the fMRI experiment) before the subsequent trial began.

## Experiment 2 – Effects of social pain based on romantic rejection

### *Participant screening*

Experiment 2 examined the effect of social pain due to romantic rejection on the perception of physical pain. The recruited participants had recently experienced an unwanted break-up (i.e., they are the ones who are rejected), and their feelings of social pain were induced by viewing photographs of their ex-partner.[16] Participants were screened using questions regarding their past romantic relationships, with the same screening process used in Experiments 3 and 4 as well. Specifically, participants were asked: (1) When did your romantic relationship with your ex-partner begin? (2) How long did your relationship last? (3) Why did your relationship end? (4) To what extent did you feel rejected by your ex-partner in the breakup experience? (Response rated from 1 = *not at all rejected* to 7 = *extremely rejected*). (5) How did you feel during the breakup? (6) How do you feel about your ex-partner now? (7) Did you still love your ex-partner when you broke up? (Response options: 1 = *not in love*, 2 = *unsure/it's complicated*, 3 = *still in love*). (8) If given the chance, would you get back together with your ex-partner now? (Response options: 1 = *no*, 2 = *unsure*, 3 = *yes*).

### *Social pain stimuli*

Before the day of the experiment, participants were asked to send the researchers 5, 10, or 15 (depending on the participant) of their own personal digital photographs of their ex-partner, either alone or in a group photo. Using an image to cue one's recall of autobiographical experiences of rejection has been proven effective in activating social rejection-related distress.[16] The digital photographs were cropped to a uniform size (800 × 664 pixels) and, on the day of the experiment, were presented to the participants on a screen at a visual angle of 18.92 ° × 15.75 ° in the main experiment; this same procedure was followed in Experiment 3.

### *Procedure*

The experimental flow was the same as that in Experiment 1. The only difference was that before beginning the experiment, participants were encouraged to recall how they felt during their recent break-up experience as they viewed the photographs of their ex-partner. In each trial, the instruction of the S and S/PS conditions was changed into "*Please perceive the following picture carefully, and then you will be asked to rate the painful feelings, heartache, and suffering caused by the photograph*". This same procedure was followed in Experiments 3 and 4.

## Experiment 3 – Reproducibility of intra-individual effects of social pain

The first two experiments had successfully revealed the general effects of social pain across various paradigms and samples. Thus, Experiment 3 examined these effects further to determine whether they were stable and could be reproduced across time periods. The full experiment required participants to come to the laboratory twice. After they had attended the first laboratory session, a second session was scheduled at least seven days later, but within two weeks of the first session (i.e., 9.19 $\pm$ 3.29 days). The procedure in the first laboratory session followed the same steps as in Experiment 2, except that only the high intensity stimuli were used to minimize the duration of the experiment. This procedure was repeated for the second laboratory session.

## Experiment 4 – Neural mechanism of the effects of social pain

### *Procedure*

Experiment 4 explored the underlying brain mechanisms engaged in the effects that had been observed in the previous behavioral experiments. Before the day of the experiment, each participant was asked to provide researchers with six digital photographs of their ex-partner, either alone or in a group shot. All pictures were cropped to a uniform size of 800 × 664 pixels and, during the experiment, were shown on a screen at a visual angle of 19.52 ° × 16.29 °. The experimental procedure followed the same steps as Experiment 2, except that only high intensity stimulus was used due to participants' potential adaptation to the pain of the low-intensity stimulus in the low-temperature environment of the scanner room.

### *Data acquisition*

A Siemens 3.0 T scanner (MAGNETOM Prisma, Siemens Healthcare GmbH, Germany) with a 64-channel head matrix coil was used for functional brain imaging. Scan sessions began with transversal localization and sequential multi-slice mode. Functional data were acquired through an echo-planar imaging sequence using a transversal orientation covering the whole brain (46 slices, TR/TE = 1500/30ms, slice thickness = 3mm, FOV = 192mm, matrix size = 94 × 94, in-plane resolution = 2 × 2mm$^2$, MultiBand = 2, GRAPPA = 2). A high-resolution T1-weighted 3D MPRAGE structural image was acquired between the first and second fMRI sessions (transversal orientation, 192 slices, TR/TE = 1900/3.97ms, FOV = 192mm, resolution = 1 × 1 × 1mm$^3$). The fieldmap (transversal orientation, 49 slices, TR/$\Delta$TE = 248/2.46ms, FOV = 192mm, resolution = 2 × 2 × 2mm$^3$) was acquired between the second and third fMRI sessions.

### *Whole-brain analysis*

On the individual level, the following preprocessing steps were applied using FMRI Expert Analysis Tool (FEAT, Version 6.00): motion correction using MCFLIRT,[37] non-brain removal using BET,[38] spatial smoothing using a Gaussian kernel of FWHM 5mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering, and ICA decomposition using MELODIC. Registration from functional images to high-resolution structures was performed using FLIRT.[37,39] Registration from high-resolution structural space to standard space was further refined using FNIRT nonlinear registration.[40,41] Then, the filtered functional data were manually de-noised following the criteria proposed by Kelly et al. (2010).[42] Each session of fMRI data were modeled on a voxel-by-voxel basis through a GLM approach,[43] while parameter estimates (PE) were obtained for each of the four conditions (i.e., P, S, P/PS, S/PS). A second-level analysis of the fixed-effects model was performed using within-subject activations across the three sessions. Finally, a group-level analysis was performed using a mixed-effects approach (FLAME),[44,45] while $Z$ (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $p = 0.05$. One-way repeated-measures analysis of variance and the independent sample T-test were performed across the subjects to investigate the brain regions involved in the variability of responses under different conditions.

### *ROI analysis*

The brain regions activated in the four conditions (i.e., P, S, P/PS, S/PS) and the brain regions with significant activation differences in the contrasts (i.e., S < P, P < S, P < P/PS, S/PS < P, S/PS < P/PS, P/PS < S/PS) were carried forward into the region of interest (ROI) analysis. ROI masks were created in FSLeyes and further thresholded by Harvard-Oxford cortical and subcortical atlases. The ROI masks were warped back to individual fMRI spaces, and average PE values within the ROIs were extracted for each subject to explore their correlation with the subjective pain ratings reported by participants during the task performed while in the scanner.

### *Whole-brain correlation analysis*

To explore the mechanism involved in the facilitatory/inhibitory effects, a GLM was using the facilitatory-related effect (i.e., the demeaned pain rating in the P/PS condition) or the inhibitory-related effect (i.e., the demeaned pain rating in the S/PS condition) as regressors of interest

to determine the facilitated/inhibited brain activation across the whole brain. Statistical images for encoding activation were thresholded using a cluster-forming correction determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

### *Psychophysiological interaction analysis*

Brain regions that were significantly correlated with pain rating (i.e., the posterior insula and the frontal pole) were investigated further using ROI masks for further PPI analyses. First, the mean timecourse was extracted from the posterior insula seed region using preprocessed functional data. Next, the timecourse was added to the GLM at the individual level as the physiological regressor, with the original task regressors as the psychological regressors. The final interaction regressor was the scalar product of the psychological and physiological regressors. Individual PEs for psychophysiological interaction were then used for the normal higher-level group comparison. We also performed a similar PPI analysis using the frontal pole as the seed. These analyses allowed us to test functional connectivity associated with either pain perception or social rejection. Based on the original PPI results, we further explored the increased crucial connectivity that predicted behavioral performance using the small-volume correction procedure using the thalamus as a mask (cluster $Z > 2.3$, $p < 0.05$). The results were then mapped on the cortical surfaces using BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

### *Neurological pain signature response analysis*

The weight map from the NPS pattern was applied to the contrast images.[46] The dot product of the voxel weights was computed within the predefined NPS mask and the contrast image of PE, yielding a continuous scalar value for each participant.[47] These signature response values were then tested for differences between the facilitatory and inhibitory effects of social pain on physical pain perception.

## QUANTIFICATION AND STATISTICAL ANALYSIS

Appropriate statistical analyses were chosen depending on the experimental setting and data type. Two-way repeated ANOVA, the independent t-test, the one-way repeated ANOVA, and the mediation analysis analyses for the behavioral data were performed using SPSS (Version 23). The ICC was also calculated by SPSS (Version 23). The correlation analyses were performed using R (Version 4.2.1). A p value % of 0.05 was considered statistically significant. The fMRI data were analyzed using FSL (Version 6.0) with a cluster-forming correction determined by $Z > 3.1$ and a corrected cluster significance threshold of $p < 0.05$.