Acetaminophen Reduces Social Pain: Behavioral and Neural Evidence

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Abstract

Pain, whether caused by physical injury or social rejection, is an inevitable part of life. These two types of pain—physical and social—may rely on some of the same behavioral and neural mechanisms that register pain-related affect. To the extent that these pain processes overlap, acetaminophen, a physical pain suppressant that acts through central (rather than peripheral) neural mechanisms, may also reduce behavioral and neural responses to social rejection. In two experiments, participants took acetaminophen or placebo daily for 3 weeks. Doses of acetaminophen reduced reports of social pain on a daily basis (Experiment 1). We used functional magnetic resonance imaging to measure participants' brain activity (Experiment 2), and found that acetaminophen reduced neural responses to social rejection in brain regions previously associated with distress caused by social pain and the affective component of physical pain (dorsal anterior cingulate cortex, anterior insula). Thus, acetaminophen reduces behavioral and neural responses associated with the pain of social rejection, demonstrating substantial overlap between social and physical pain.

Suffering social rejection may seem completely different from suffering physical injury, but recent evidence suggests that the pain of social rejection and physical pain are interconnected. People who feel socially rejected often describe their feelings using words that are typically associated with physical pain, complaining, for example, of hurt feelings. In fact, the use of physical-pain words to describe one's feelings following social rejection is common to many languages, indicating a potentially universal phenomenon (MacDonald & Leary, 2005). Is the pain of social rejection (social pain; MacDonald, 2009) truly comparable to physical pain, or is the expression merely metaphorical? If the similarities between physical and social pain are more than just metaphorical, can researchers alleviate social pain with medications typically used to reduce physical pain? The current experiments provide the first direct evidence that answers these questions.

Studies suggest that the similar linguistic descriptions of social and physical pain extend beyond metaphor, and demonstrate overlap in the neurobiological systems underlying physical pain and social pain (DeWall & Baumeister, 2006;

Eisenberger, Lieberman, & Williams, 2003; Way, Taylor, & Eisenberger, 2009). In the present experiments, we examined one functional consequence of the hypothesis that social and physical pain rely on shared neurobiological systems—whether acetaminophen, a common physical pain reliever, also reduces social pain. We tested the hypothesis using behavioral (Experiment 1) and functional magnetic resonance imaging (fMRI; Experiment 2) methods in two independent samples.

Overlap of Social and Physical Pain

Overlapping social and physical pain systems probably conferred an advantage among our evolutionary ancestors. Because many mammalian species have an extended infancy—during

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which young are unable to defend or feed themselves—maintaining social connections from an early age is critical for survival. The social attachment system in humans may have evolved by piggybacking directly onto the physical pain system to promote survival (Panksepp, 1998). To the extent that social separation threatened human survival, feeling hurt by separation may have offered an adaptive edge. Indeed, some of the same brain regions involved in the affective experience of physical pain are also involved in the experience of social pain (Eisenberger et al., 2003).

Neuroimaging studies of the affective or unpleasant component of physical pain typically involve brain regions such as the dorsal anterior cingulate cortex (dACC) and anterior insula (Apkarian, Bushnell, Treede, & Zubieta, 2005; Peyron, Laurent, & Garcia-Larrea, 2000; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Patients with lesions in these regions report that they are not bothered by physically painful stimuli, even though they can still perceive these stimuli (Berthier, Starkstein, & Leiguarda, 1988; Foltz & White, 1962; Hebben, 1985). It is significant that these neural regions are also associated with experiences of social rejection or social loss in humans, and separation distress behaviors in nonhuman mammals. For example, in nonhuman primates that have been separated from caregivers or the social group, lesions to the ACC (both dorsal and ventral subdivisions) attenuate distress vocalizations (Hadland, Rushworth, Gaffan, & Passingham, 2003; MacLean, & Newman, 1988), whereas electrical stimulation of these regions elicits distress vocalizations (Robinson, 1967; W.K. Smith, 1945). Similarly, in humans, experiences of social rejection increase activity in the dACC and anterior insula (Eisenberger et al., 2003). Moreover, simply viewing pictures of lost loved ones activates the same neural regions in bereaved individuals (O'Connor et al., 2008).

Can Acetaminophen Reduce Social Pain?

One implication of an overlap in the neural systems underlying physical pain and social pain is that factors that reduce physical pain should have a parallel effect on social pain. In this investigation, we examined whether acetaminophen, a well-known physical pain reliever, could also reduce the pain experienced as a result of social rejection. Although the precise mechanisms by which acetaminophen exerts an analgesic effect are still unclear, it is widely accepted that acetaminophen reduces pain through central, rather than peripheral, nervous system mechanisms (Anderson, 2008; H.S. Smith, 2009). Thus, acetaminophen may reduce the experience of social pain by attenuating neural activity in brain regions known to play a role in physical as well as social pain processes (i.e., dACC, anterior insula).

To examine the effect of acetaminophen on the experience of social pain and underlying neural correlates, we conducted two experiments. In Experiment 1, we used an experience-sampling method to examine whether a daily dose of acetaminophen (vs. placebo) over a 3-week period reduced participants' daily experiences of social pain or *hurt feelings* (the core emotional response to social rejection; Leary, Springer, Negel, Ansell, & Evans, 1998). In Experiment 2, we used functional magnetic resonance imaging (fMRI) to examine whether a daily dose of acetaminophen (vs. placebo) over a 3-week period reduced social-pain-related neural activity (i.e. in dACC, anterior insula) when participants were exposed to a discrete episode of social rejection at the end of the 3-week period.

Experiment 1

In Experiment 1, we carried out a preliminary test of the hypothesis that acetaminophen reduces hurt feelings. Participants took acetaminophen or placebo in pill form each day for 3 weeks and reported their hurt feelings daily. We predicted that acetaminophen would reduce the intensity of participants' psychological hurt feelings over time, whereas no such reduction would be observed in participants who had taken placebo.

Method

Participants. Sixty-two healthy undergraduates participated in this experiment (see the Supplemental Material available online for the exclusion criteria).

Materials and procedure. Participants took one 500-mg pill immediately after waking up each day, and another 500-mg pill an hour before going to sleep. By random assignment, about half of the participants ($n = 30$; 24 women, 6 men) ingested a daily dose of 1,000 mg of acetaminophen, and the other half ($n = 32$; 24 women, 8 men) took the same dose of placebo. Each evening, participants used the Hurt Feelings Scale (Leary & Springer, 2001), specifically the today version (e.g., "today, being teased hurt my feelings"), to report how much social pain they had experienced that day. Leary and Springer (2001) showed that this measure of hurt feelings relates specifically to the experience of social exclusion and cannot be reduced to other negative emotions. Participants also provided a daily measure of general positive emotion they had experienced during the same day (e.g., happy, content; Mayer & Gaschke, 1988), which allowed us to test whether acetaminophen alters positive emotional experience.

Results and discussion

Because our data were nonindependent (days were nested within participants), we used multilevel modeling. As predicted, participants' hurt feelings decreased significantly over time in participants who took acetaminophen, average slope = –0.0081, $t(60) = -2.10$, $p < .05$, $d = -0.54$ (see Fig. 1). In contrast, participants who took the placebo showed no change over time in their daily hurt feelings: average slope = 0.0035, $t(60) = 0.60$, $p > .55$, $d = 0.15$. At Day 1, the acetaminophen
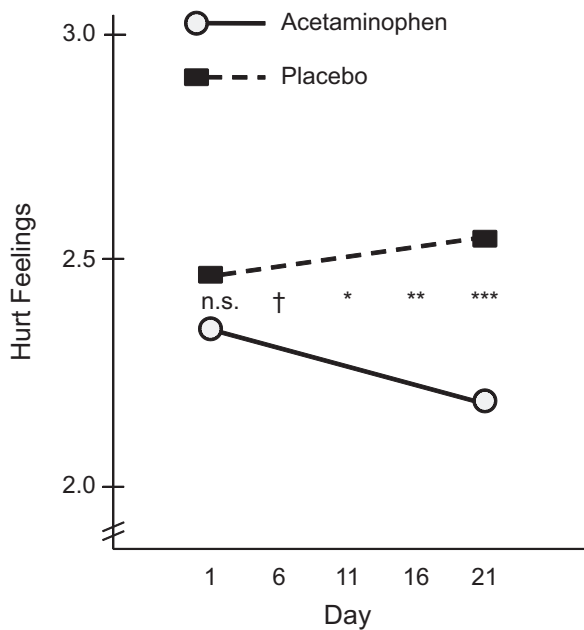
Fig. 1. Participants' hurt feelings (according to the Hurt Feelings Scale; Leary & Springer, 2001) in Experiment 1 as a function of the time of assessment (Day 1 through Day 21), for both the placebo group and the acetaminophen group. The statistical result for the between-groups comparison is given for each day ($^\dagger p < .10$, $^*p < .05$, $^{**}p < .01$, $^{***}p < .005$).

and placebo groups did not differ: average difference $= -0.14$, $t(60) = -1.02$, $p > .30$, $d = -0.26$; however, at Day 21, the acetaminophen group had significantly lower hurt feeling scores than those in the placebo group: average difference $= -0.38$, $t(60) = -2.94$, $p < .005$, $d = -0.76$. More specifically, from Day 9 ($p < .05$) to Day 21 ($ps < .05$), participants in the acetaminophen group reported significantly lower daily hurt feelings on average than participants in the placebo group: The difference in change-over-time slopes between the two groups was marginally significant: interaction coefficient $= -0.012$, $t(60) = -1.66$, $p \le .10$, $d = -0.43$. In contrast, drug condition did not moderate the change-over-time slopes for daily positive emotion, $p > .20$. Neither the acetaminophen group nor the placebo group had significant change-over-time slopes for daily positive emotion (both $ps > .40$). These data provide the first evidence that a daily dose of acetaminophen can decrease self-reported hurt feelings over time. Our results also demonstrate that acetaminophen acts on emotions that are associated with social pain, rather than via boosting or suppressing positive emotion.

Experiment 2

In Experiment 2, we examined the neural mechanisms by which acetaminophen reduces hurt feelings. Participants took 2,000 mg of either acetaminophen or placebo in pill form for 3 weeks, and then completed a social exclusion task while undergoing an fMRI scan. We hypothesized that participants who took acetaminophen would show less activity during social rejection in regions of the brain previously shown to respond to social pain (i.e., dACC, anterior insula) than participants who took placebo.

Method

Participants. Twenty-five healthy, right-handed undergraduates participated in this experiment.

Materials and procedure. Participants took two 500-mg pills immediately after waking up each day and two 500-mg pills an hour before going to sleep. By random assignment, participants ingested a daily dose of 2,000 mg of acetaminophen ($n = 10$; 6 women, 4 men) or placebo ($n = 15$; 10 women, 5 men). We doubled the daily dose administered in Experiment 1 to counteract the decreased statistical power due to the smaller sample size in Experiment 2.

After 3 weeks, participants arrived at the imaging center believing they would complete a virtual ball-tossing game (Cyberball; Williams, Cheung, & Choi, 2000) with two other same-sex participants, each in fMRI scanners. In reality, participants played with a preset computer program. In Round 1 of the game, participants were included for the entire duration of the game. In Round 2, participants were excluded after receiving the ball three times, and the other two players stopped throwing the ball to them (see the Supplemental Material available online for additional details on the procedure for this game). After completing the imaging portion of the study, participants completed a measure of self-reported social distress, which assessed their feelings in response to the exclusion episode (e.g., "I did not feel accepted by the other players"; Williams et al., 2000).

fMRI procedure and analyses. Data were aquired on a 3-T Siemens Trio scanner (Siemens, Erlangen, Germany) at the University of Kentucky. Functional neuroimaging data were collected during each round of the ball-tossing game using a T2*-weighted gradient echo sequence with the following parameters: 30 ms of echo time, 64 × 64 matrix, 224-mm × 224-mm field of view, 40 3.5-mm axial slices acquired in interleaved order at a 2-s repetition time. These parameters allowed whole brain coverage with 3.5-mm cubic voxels. A 3-D shim was performed before all EPI (echo planar imaging) image acquisitions. The neuroimaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England; see the Supplemental Material for further details).

On the basis of a priori hypotheses regarding the involvement of the dACC and anterior insula in the overlap between social and physical pain processes, we utilized structurally defined region-of-interest (ROI) analyses to examine between-group differences in neural activity in these two regions during an experience of social exclusion, compared to an experience

of social inclusion (*p* < .05). To more fully explore the neural regions affected by acetaminophen, we supplemented ROI analyses with a whole-brain analysis. Thus, we ran a between-groups *t* test comparing neural activity in the acetaminophen group with that in the placebo group during social exclusion (vs. social inclusion) at each voxel across the entire brain volume (*p* < .005, 20-voxel extent threshold; Lieberman & Cunningham, 2009). All coordinates are reported in Montreal Neurological Institute format. (See the Supplemental Material for additional details on data analyses and ROI construction.)

Results and discussion

As predicted, ROI analyses revealed that participants who took acetaminophen, compared with those who took placebo, showed significantly less activity in the dACC, *t*(23) = 2.13, *p* < .05, *d* = 0.89, and bilateral anterior insula, *t*(23) = 2.31, *p* < .05, *d* = 0.96, in response to social exclusion versus social inclusion (Fig. 2). Results from the whole-brain analyses were consistent with those from the ROI analyses: Participants who took acetaminophen, compared with those who took placebo, showed significantly less dACC activity in two regions: [9, 27, 21], *t*(23) = 3.74, *p* < .0005, *d* = 1.56 (Fig. 3a), and [−9, −6, 45], *t*(23) = 4.42, *p* < .0001, *d* = 1.84, and significantly less right anterior insula activity, [45, 21, −9], *t*(23) = 3.28, *p* < .005, *d* = 1.37 (Fig. 3b), in response to social exclusion versus inclusion.

Participants who took acetaminophen also showed significantly less activity than those who took placebo in other brain regions that have been linked with affective processes, including the bilateral posterior insula, [45, 0, −18], *t*(23) = 5.31, *p* < .0001, *d* = 2.21; [−39, −3, −6], *t*(23) = 4.69, *p* < .0001, *d* = 1.96; and the right amygdala, [27, 0, −15], *t*(23) = 3.29, *p* < .005, *d* = 1.37 (see Table 1 for the complete list of activated areas). Participants who took acetaminophen did not show greater neural activity than participants who took placebo in any of the regions. Thus, in addition to reducing self-reported hurt feelings over time (Experiment 1), acetaminophen (vs. placebo) reduced social-pain-related neural responses to a discrete episode of social rejection.

Although acetaminophen reduced activation in regions associated with the affective component of pain (in both ROI and whole-brain analyses), participants in both the acetaminophen and control groups reported equal levels of social distress in response to the exclusion episode, *F*(1, 24) = 1.43, *p* = .24. Thus, our neuroimaging findings supported our prediction that acetaminophen would reduce dACC and anterior insula activation to social exclusion (vs. social inclusion). The self-report measure of social distress did not conform to predictions.

General Discussion

Our findings provide converging evidence for an overlap between the body's systems for responding to social and
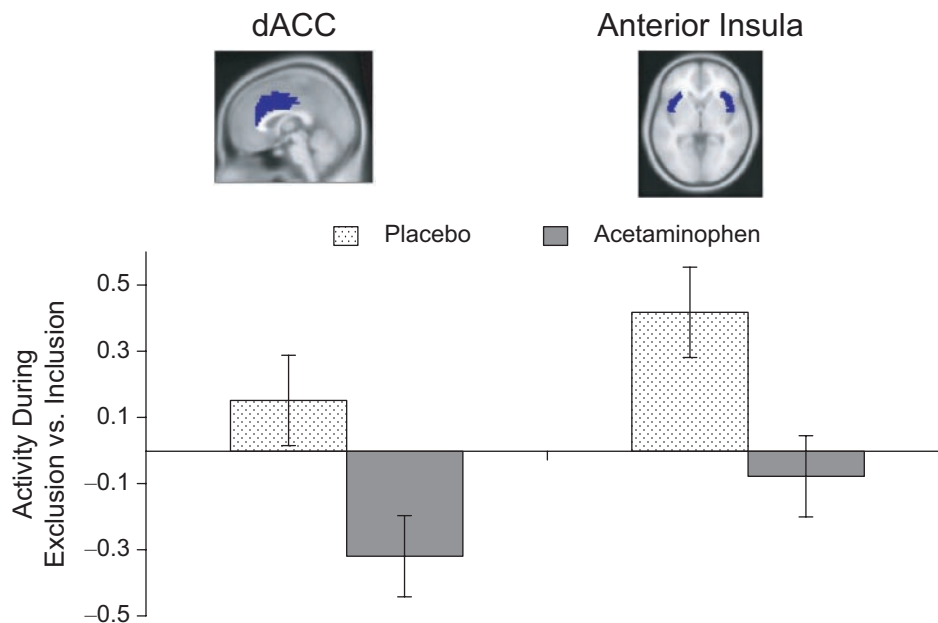

Fig. 2. Results from the region-of-interest analysis in Experiment 2: change in neural activity (parameter estimates during social exclusion vs. social inclusion) in the dorsal anterior cingulate cortex (dACC; left) and bilateral anterior insula (right) in participants who took acetaminophen and those who took placebo. Each structurally defined region of interest is highlighted in blue in the illustration above the corresponding bar graph. Error bars represent standard errors.
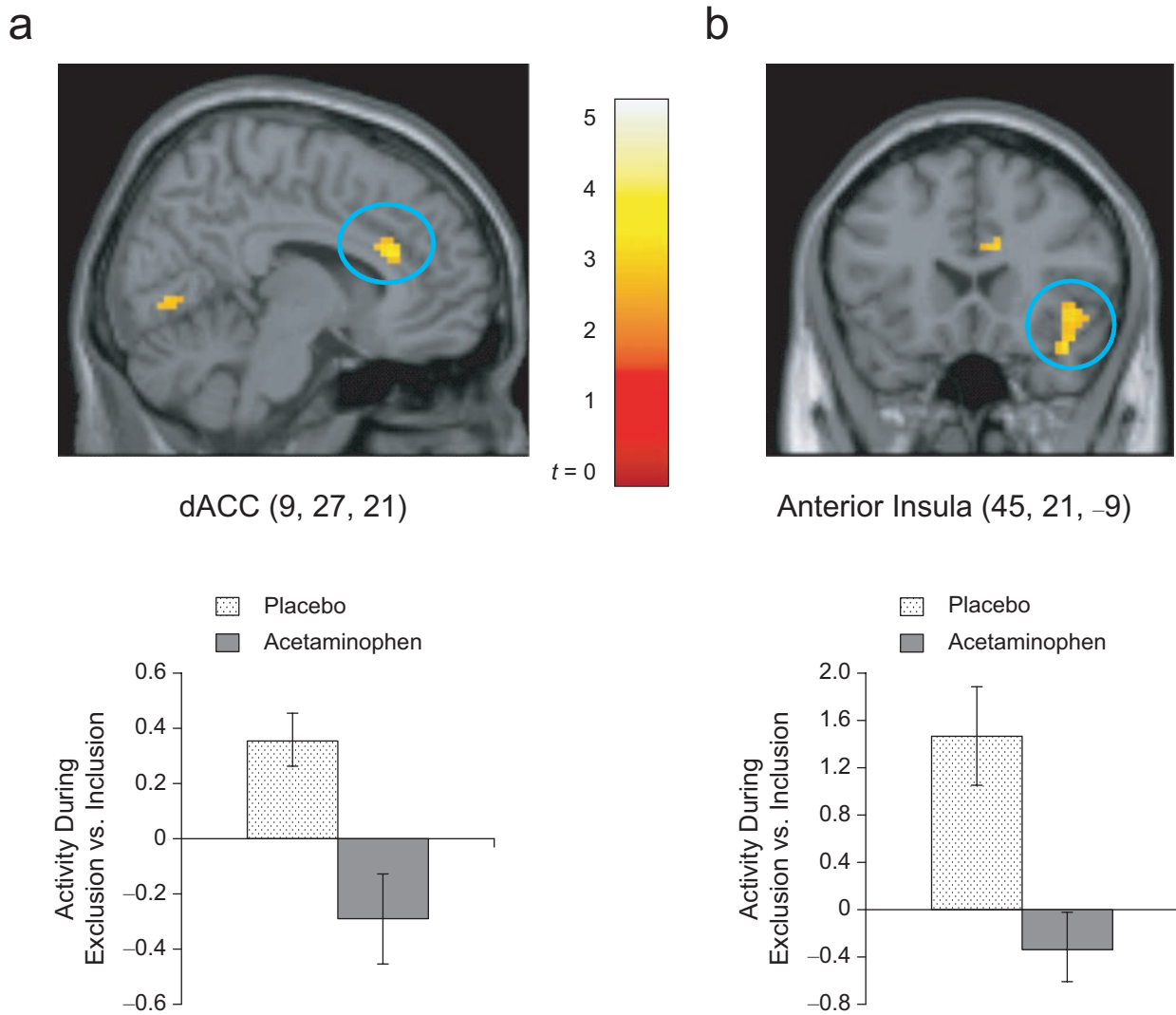
Fig. 3. Results from the whole-brain, between-groups analysis in Experiment 2: change in neural activity (parameter estimates during exclusion vs. inclusion) in (a) dorsal anterior cingulate cortex (dACC) and (b) right anterior insula in participants who took acetaminophen and those who took placebo. Error bars represent standard errors. Comparisons were calculated using a significance level of $p < .005$, with a 20-voxel extent threshold. The illustration above each graph shows change in intensity of neural activity that was greater for participants who took placebo than for those who took acetaminophen (see the color bar); results are averaged across the entire cluster and both conditions. The circled regions are those for which results are given in the bar graphs.

physical pain. We found that daily doses of acetaminophen, a painkiller used to reduce physical pain, diminished daily psychological hurt feelings. Acetaminophen, compared with placebo, also decreased neural activity in response to social rejection in brain regions previously shown to be associated with experiencing social pain and the affective component of physical pain.

Social exclusion is a common part of life, which underscores the implications of our findings. People can feel ostracized at work, snubbed by friends, or excluded by close partners. For some, social exclusion is an inescapable and frequent experience (Williams, 2001). Our findings suggest that an over-the-counter painkiller normally used to relieve physical aches and pains can also at least temporarily mitigate social-pain-related distress.

Furthermore, many studies have shown that being rejected can trigger aggressive and antisocial behavior, which could lead to further complications in social life (DeWall, Twenge, Gitter, & Baumeister, 2009; Warburton, Williams, & Cairns, 2006). If acetaminophen reduces the distress of rejection, the behavioral consequences of rejection, such as antisocial behavior, may be reduced as well. Indeed, our fMRI results showed that acetaminophen diminished reactivity in the dACC and amygdala, brain regions that have been linked to aggression (Denson, Pedersen, Ronquillo, & Nandy, 2009; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). It would therefore be worthwhile to explore whether acetaminophen reduces the aggressive consequences of social rejection. Our findings do not warrant the widespread use of acetaminophen to cope with

Table 1. Results From Experiment 2: Regions With Greater Differential Neural Activity During Social Exclusion (vs. Inclusion) in Participants Who Took Placebo Than in Those Who Took Acetaminophen

Anatomical brain region	Brodmann's area	Hemisphere	Montreal Neurological Institute coordinates			t score (local maxima)	No. of voxels	p
			x	y	z			
Dorsal anterior cingulate cortex	24/32	Right	9	27	21	3.74	50	< .0005
Dorsal anterior cingulate cortex	24	Left	-9	−6	45	4.42	38	< .0001
Anterior insula		Right	45	21	−9	3.28	481	< .005
Posterior insula		Right	45	0	−18	5.31	481	< .0001
Posterior insula		Left	−39	−3	−6	4.69	212	< .0001
Amygdala		Right	27	0	−15	3.29	481	< .005
Temporal pole	38	Right	30	12	−27	5.54	481	< .0001
Hippocampus		Right	27	−39	−6	4.80	87	< .0001
Hippocampus		Right	27	−21	−18	4.66	109	< .0001
Dorsolateral prefrontal cortex	46	Left	−33	27	24	4.36	37	< .0005
Motor cortex	4	Left	−63	−12	27	3.56	27	< .001
Motor cortex	4	Right	54	−9	24	3.46	26	< .001
Posterior superior temporal sulcus	22	Left	−54	−36	12	4.09	63	< .0005
Putamen		Right	24	−6	3	3.82	34	< .0005
Occipital lobe	18	Left	−3	−81	−3	3.48	124	< .001
Ventrolateral prefrontal cortex		Right	48	45	15	3.25	33	< .005
Cerebellum		Right	42	−60	−21	4.04	34	< .0005
Cerebellum		Left	−12	−42	−6	3.20	47	< .005

Note: Each voxel is 3.5 mm^3. Comparisons were calculated using a significance level of $p < .005$, with a 20-voxel extent threshold.

all personal problems. Future research is needed to verify the potential benefits of acetaminophen in reducing emotional and antisocial responses to social rejection.

One limitation to the work presented here is that we did not include an experimental condition in which participants experienced physical pain. Future research should examine whether acetaminophen affects the same neural regions in response to both physical and social pain. Other research avenues include investigating potential dose-dependent responses to acetaminophen in reducing social pain, and the time course of such relationships. Acetaminophen has a relatively short half-life, lasting approximately 4 hr (Pappas, Taylor, & Ackerman, 1991), which means that it is unlikely that acetaminophen had a cumulative effect in our experiments. Our finding that acetaminophen reduced hurt feelings over time could be due to a combination of not feeling hurt and having a greater ability to reappraise the rejection experience. Future research should be aimed at exploring the acute effects of acetaminophen on social responses in addition to the mechanism underlying the longitudinal effects we observed.

The current investigation provides novel insight into the close relationship between social and physical pain, by exploring one surprising consequence of the hypothesis that physical and social pain rely on shared neurobiological substrates. We have shown for the first time that acetaminophen, an over-the-counter medication commonly used to reduce physical pain, also reduces the pain of social rejection, at both neural and behavioral levels.

Supplemental Material

Additional supporting information may be found at http://pss.sagepub.com/content/by/supplemental-data

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