

Over-the-Counter Relief From Pains and Pleasures Alike: Acetaminophen Blunts Evaluation Sensitivity to Both Negative and Positive Stimuli

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Abstract

Acetaminophen, an effective and popular over-the-counter pain reliever (e.g., the active ingredient in Tylenol), has recently been shown to blunt individuals' reactivity to a range of negative stimuli in addition to physical pain. Because accumulating research has shown that individuals' reactivity to both negative and positive stimuli can be influenced by a single factor (an idea known as *differential susceptibility*), we conducted two experiments testing whether acetaminophen blunted individuals' evaluations of and emotional reactions to both negative and positive images from the International Affective Picture System. Participants who took acetaminophen evaluated unpleasant stimuli less negatively and pleasant stimuli less positively, compared with participants who took a placebo. Participants in the acetaminophen condition also rated both negative and positive stimuli as less emotionally arousing than did participants in the placebo condition (Studies 1 and 2), whereas nonevaluative ratings (extent of color saturation in each image; Study 2) were not affected by drug condition. These findings suggest that acetaminophen has a general blunting effect on individuals' evaluative and emotional processing, irrespective of negative or positive valence.

Keywords

acetaminophen, evaluation, attitudes, affect, emotion, differential susceptibility

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When people experience pain, one of the most common treatments they reach for is acetaminophen (the active ingredient in Tylenol). From dental pains to ankle sprains, acetaminophen is an effective pain reliever for a wide variety of physical ailments. It is thus unsurprising that acetaminophen is the most popular over-the-counter means of pain relief in the United States, being taken by an estimated 50 million Americans each week (Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002).

Recent psychological evidence has provocatively demonstrated that acetaminophen reduces individuals' sensitivity to a range of negative stimuli beyond bodily aches and pains. When taken over the course of 3 weeks, for instance, acetaminophen (compared with a placebo) blunts hurt feelings that individuals report experiencing in their social relationships (DeWall et al., 2010). This finding is consistent with prior notions that pains originating from both physical and

social sources share common neurochemical underpinnings (Panksepp, 1998).

A one-time dose of acetaminophen likewise attenuates individuals' negative reactions to emotionally evocative stimuli. Specifically, work by Randles, Heine, and Santos (2013) suggested that participants who received an acute dose of acetaminophen experienced less negativity when thinking about their own mortality than did participants who received a placebo. Recent findings have likewise shown that acetaminophen can reduce the discomfort that

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people experience when making difficult decisions (DeWall, Chester, & White, 2015).

Acetaminophen: Psychological Mechanisms of Action

These intriguing findings raise a pertinent question: How can a pain reliever have an ameliorating effect on such a wide range of negative experiences, painful or otherwise? Though which specific neurochemical pathways are affected by acetaminophen is not entirely clear (Anderson, 2008; Pini, Sandrini, & Vitale, 1996; Smith, 2009), accumulating evidence indicates that the brain is a critical site (Graham, Davies, Day, Mohamudally, & Scott, 2013). Therefore, one potential mechanism explaining these effects is that acetaminophen alters one or more psychological processes, which in turn affects the magnitude of individuals' evaluations of any negative stimulus. In this sense, the process of evaluation—that is, associating a stimulus with some degree of negativity, positivity, or both (Cacioppo & Berntson, 1994)—may be affected by the neurochemical effects of acetaminophen in the brain.

Indeed, a wide variety of existing theories and empirical research suggest that if acetaminophen attenuates negative evaluations, it may likewise blunt positive evaluations. For instance, individuals scoring lower in emotional expressivity (Gross & John, 1997, 1998), affect intensity (Larsen, 2009), or their need for affect (Maio & Esses, 2001) will react less extremely to both negative and positive experiences (e.g., Britt, Millard, Sundareswaran, & Moore, 2009; Schimmack & Diener, 1997; Suh, Diener, & Fujita, 1996). These findings are broadly consistent with data from neuroscience showing that negative and positive reactions are each associated with shared brain networks that are critical for evaluative and emotional processing (Berntson et al., 2011; Craig, 2009; Lindquist & Barrett, 2012). For example, Berntson and colleagues (2011) examined how insula damage (relative to damage to the amygdala or control regions) affected individuals' evaluations of negative and positive images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). Results indicated that insula damage led to reduced negative evaluations of unpleasant stimuli and reduced positive evaluations of pleasant stimuli. This reduction in the extremity of both negative and positive evaluations following insula damage is intriguing in light of evidence indicating that acetaminophen attenuates activity in the insula and other brain regions (DeWall et al., 2010).

We propose that an idea originally arising from developmental psychology—specifically, the theory of differential susceptibility (Belsky & Pluess, 2009)—provides a parsimonious theoretical framework for understanding these diverse but consistent observations of individuals'

evaluative sensitivity to both negative and positive stimuli. The theory of differential susceptibility predicts that the same individuals who are more likely to struggle in negative, stressful environments might also be more likely to thrive in positive, nurturing environments (see Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007). It therefore follows that individuals who are less sensitive to negative experiences are likewise less responsive to positive experiences. As a result—and consistent with individual differences in emotional expressivity, affect intensity, and need for affect—past research that has examined psychological processes that lead people to be more or less sensitive to negative information may in fact be describing factors that cause individuals to be differentially sensitive to both negative and positive influences.

These observations suggest that the previously observed blunting effects of acetaminophen on various negative evaluations may represent only half the story. Specifically, acetaminophen may be exerting a broader attenuating effect on individuals' evaluative and emotional processing of stimuli presented in their environment, be they painful or pleasant in nature. Therefore, we propose that this drug may more generally blunt the extremity of all evaluations, especially toward increasingly emotionally evocative stimuli. That is, contrary to existing assumptions, acetaminophen may actually reduce positive reactions as well as negative ones.

Overview of the Present Research

On the basis of existing theories and evidence of broader evaluative and emotional sensitivity, we predicted that people taking acetaminophen would experience blunted negative reactions to unpleasant stimuli and blunted positive reactions to pleasant stimuli, compared with people taking a placebo. Our first study was designed as an initial test of this hypothesis and was modeled on the aforementioned study of patients with insula lesions (Berntson et al., 2011). A second, essentially identical study was conducted not only to replicate these findings, but also to test whether the effects of acetaminophen were unique to evaluative judgments or whether acetaminophen might affect any and all judgments of relative magnitude (e.g., the degree of color saturation). In accord with recently recommended approaches to presenting the results of multiple studies through combined analyses (Eich, 2014), we collapsed the results of the two studies and submitted participants' evaluations, self-reports of emotional arousal (Studies 1 and 2), and judgments about color saturation (Study 2) to the same between-within-participants mixed-model analyses.

Method

Eighty-two participants in Study 1 and 85 participants in Study 2 were recruited to participate in an experiment on

“Tylenol and social cognition” in exchange for course credit. Our stopping rule of at least 80 participants per study was based on previously published research on acetaminophen (DeWall et al., 2010; Randles et al., 2013), in which 30 to 50 participants were recruited per condition (i.e., acetaminophen vs. a placebo). All procedures were identical across the two studies except where noted. The analyses reported here for the combined studies are reported for each study separately in the Supplemental Material available online.

Stimuli

Forty pictures from the IAPS were used as stimuli. These pictures were selected a priori from five categories based on normative evaluations (Berntson et al., 2011; Lang et al., 2008). These consisted of 10 extremely unpleasant stimuli (IAPS IDs: 2205, 2683, 2730, 2800, 3301, 3530, 6350, 9040, 9300, 9571), 5 moderately unpleasant stimuli (IAPS IDs: 1270, 2590, 2694, 5971, 9001), 10 neutral stimuli (IAPS IDs: 1670, 2372, 2570, 5395, 5520, 7000, 7041, 7175, 7186, 7224), 5 moderately pleasant stimuli (IAPS IDs: 1450, 1602, 2510, 2791, 5711), and 10 extremely pleasant stimuli (IAPS IDs: 2040, 2091, 4626, 4660, 5470, 7502, 8185, 8190, 8200, 8501). These stimuli depict a variety of social and nonsocial contexts and experiences.

Procedure

Participants were randomly assigned to take either an acute dose of 1,000 mg of acetaminophen or a placebo, both in a liquid vehicle. Experimenters and participants were unaware of participants' assignment to condition. After a 60-min waiting period to allow acetaminophen to enter the brain (Anderson, 2008; Singla et al., 2012; Smith, 2009), participants completed all relevant measures on computers within individual cubicles.

First, the 40 pictures from the IAPS were presented in a random order, and participants evaluated each stimulus by responding to the question, “To what extent is this picture positive or negative?” using an 11-point scale from -5 (*extremely negative*) to 5 (*extremely positive*). Then, participants saw all 40 images once more in a different random order and rated their level of emotional arousal by responding to the question, “To what extent does this picture make you feel an emotional reaction?” using an 11-point scale from 0 (*I feel little to no emotion*) to 10 (*I feel an extreme amount of emotion*; Berntson et al., 2011). For both measures, each stimulus was present on screen until participants responded. Eight participants in Study 1 (3 in the acetaminophen condition, 5 in the placebo condition) and 6 participants in Study 2 (2 in the acetaminophen condition, 4 in the placebo condition) responded to at least one of the measures in less

than 500 ms and were therefore excluded from analyses, as they appeared not to be taking the study seriously.

In Study 2, after evaluating and indicating their emotional arousal toward each stimulus, participants saw all images one last time, in a different randomized order. During this phase, participants were asked to respond to the question, “To what extent is the color blue represented in this picture?” using an 11-point scale from 0 (*The picture has zero blue color*) to 10 (*This picture is 100% the color blue*). This measure was designed to be structurally similar to the other measures while having participants focus on a dimension of judgment that would be minimally influenced by evaluative aspects, in order to test whether acetaminophen affects evaluations specifically or whether it blunts any and all judgments of magnitude.

From participants' responses, we computed three measures of evaluation and emotional arousal. First, participants' evaluation extremity (distance from the scale midpoint of 0; Abelson, 1995) and emotional arousal toward all 40 stimuli were averaged to create a global score for each measure. Second, participants' evaluation extremity and emotional arousal toward neutral, moderate (both positive and negative), and extreme (both positive and negative) stimuli were computed in order to analyze how stimulus extremity, regardless of its negative or positive normative rating, might be affected as a function of treatment. Finally, participants' raw evaluations and emotional arousal toward the stimuli were averaged within each of the five normative stimulus categories (extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant) to analyze how these measures might be affected by treatment in varying directions.

Results

At the end of Study 1, participants indicated whether they thought they took acetaminophen or a placebo, or whether they had no idea. Forty-two percent of participants responded that they did not know. Among participants who responded that they had taken one treatment over another, a chi-square test of independence was performed to examine whether actual treatment predicted participants' perceived treatment. This test yielded a marginally significant result, $\chi^2(1, N = 43) = 3.41, p = .065$. Specifically, 67% of participants who guessed that they took acetaminophen were actually in the placebo condition. In Study 2, participants were asked to indicate whether they thought they took acetaminophen or a placebo without the option to say explicitly that they did not know. A chi-square test of independence yielded a non-significant result, $\chi^2(1, N = 79) = 0.00, p = .950$. Specifically, 54% of participants who guessed that they took acetaminophen were actually in the placebo condition. These

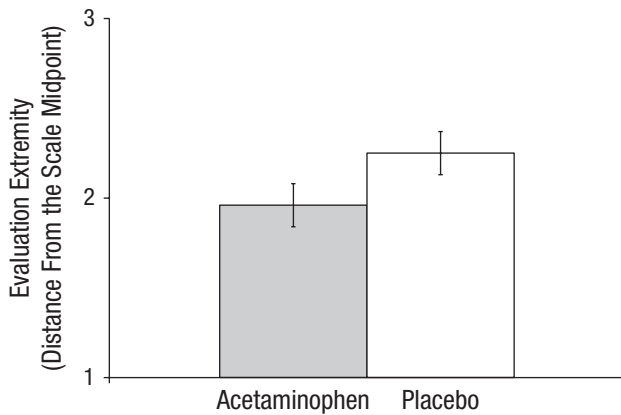


Fig. 1. Mean evaluation extremity across the two studies as a function of treatment condition. Evaluation extremity was indexed by calculating the mean rating of stimuli and then determining the distance of that rating from the scale midpoint. Error bars represent 95% confidence intervals.

results suggest that expectancy effects of treatment were not driving the findings.

Evaluations

Participants' overall evaluation extremity to all stimuli across the two studies was submitted to an independent-samples *t* test, with treatment as the between-participants factor. As expected, participants who took acetaminophen evaluated the stimuli as less extreme ($M = 1.96$, $SD = 0.56$) than participants who received a placebo ($M = 2.25$, $SD = 0.49$), $t(151) = 3.40$, $p = .001$, $\eta_p^2 = .071$ (Fig. 1).

Next, we accounted for differences between stimulus categories by submitting participants' evaluation extremity across the two studies to a 2 (treatment: acetaminophen, placebo) \times 3 (image category: neutral, moderate, extreme) mixed-model analysis of variance (ANOVA), with treatment as a between-participants factor and image category as a within-participants factor. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 16.92$, $p < .001$. Because the epsilon value was greater than 0.75 ($\epsilon = 0.92$), degrees of freedom were corrected using Huynh-Feldt estimates of sphericity. A main effect of image category was found, $F(1.8, 277.8) = 1,145.33$, $p < .001$, $\eta_p^2 = .884$. Specifically, participants rated neutral stimuli least extremely (in either a positive or negative direction), moderate stimuli relatively more extremely than neutral stimuli, and extreme stimuli relatively more extremely than moderate stimuli. These results reflected normative ratings of the stimuli.

As expected, however, this analysis yielded a main effect of treatment, $F(1, 151) = 10.43$, $p = .002$, $\eta_p^2 = .065$, and the predicted interaction of treatment and image category, $F(1.8, 277.8) = 5.32$, $p = .007$, $\eta_p^2 = .034$ (Fig. 2). Contrast analyses within each category revealed that

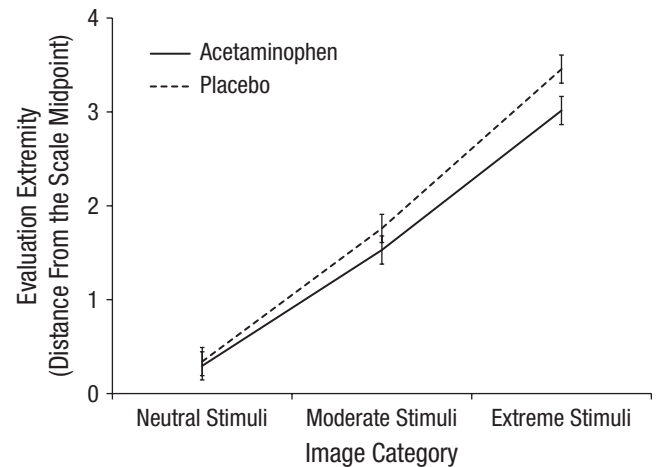


Fig. 2. Mean evaluation extremity across the two studies as a function of image category (collapsed across valence) and treatment condition. Evaluation extremity was indexed by calculating the mean rating of stimuli and then determining the distance of that rating from the scale midpoint. Error bars represent 95% confidence intervals.

participants who took acetaminophen evaluated extreme stimuli ($M = 3.01$, $SD = 0.89$) as significantly less extreme (in either a positive or negative direction) than did participants who received a placebo ($M = 3.46$, $SD = 0.71$), $t(151) = 3.38$, $p = .001$. Likewise, participants who took acetaminophen evaluated moderate stimuli ($M = 1.53$, $SD = 0.68$) as significantly less extreme than did participants who received a placebo ($M = 1.76$, $SD = 0.62$), $t(151) = 2.18$, $p = .030$. Evaluation extremity toward neutral stimuli did not differ as a function of treatment, $p = .422$.

Finally, participants' raw evaluations across studies were submitted to a 2 (treatment: acetaminophen, placebo) \times 5 (normative rating: extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant) mixed-model ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 185.78$, $p < .001$. Because the epsilon value was less than or equal to 0.75 ($\epsilon = 0.58$), degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. A main effect of normative rating was found, $F(2.3, 347.1) = 1,302.46$, $p < .001$, $\eta_p^2 = .896$. Specifically, participants rated extremely unpleasant pictures more negatively and extremely pleasant pictures more positively in a linear fashion, consistent with normative ratings of the stimuli. There was also a marginally significant main effect of treatment on evaluations, $F(1, 151) = 3.42$, $p = .066$, $\eta_p^2 = .022$, which indicated that participants who took acetaminophen tended to rate the images more negatively overall ($M = -0.25$) than did participants who took a placebo ($M = -0.17$).

These main effects were qualified by a significant interaction of treatment and normative rating, $F(2.3, 347.1) = 6.19$, $p = .001$, $\eta_p^2 = .039$ (Fig. 3), consistent with

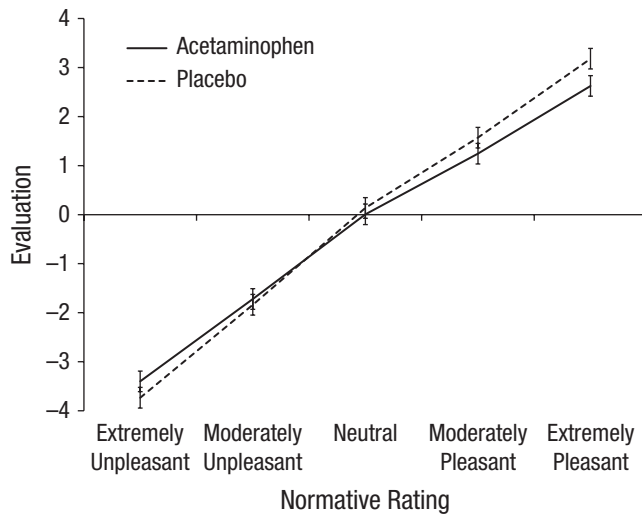


Fig. 3. Mean evaluation of stimuli across studies as a function of normative-rating category and treatment condition. Error bars represent 95% confidence intervals.

our hypothesis. Contrast analyses revealed that participants who took acetaminophen rated extremely unpleasant stimuli ($M = -3.40$, $SD = 1.00$) significantly less negatively than did participants who received a placebo ($M = -3.73$, $SD = 0.78$), $t(151) = 2.28$, $p = .024$. Likewise, participants who took acetaminophen also rated extremely pleasant stimuli ($M = 2.62$, $SD = 1.01$) significantly less positively than did participants who received a placebo ($M = 3.18$, $SD = 0.89$), $t(151) = 3.60$, $p < .001$.

Participants who took acetaminophen also rated moderately pleasant stimuli ($M = 1.24$, $SD = 0.93$) significantly less positively than participants who received a placebo ($M = 1.57$, $SD = 0.92$), $t(151) = 2.18$, $p = .031$. Finally, participants who took acetaminophen additionally tended to rate moderately unpleasant stimuli less negatively ($M = -1.72$, $SD = 0.99$) and neutral stimuli less positively ($M = 0.01$, $SD = 0.43$), compared with participants who received a placebo ($M_s = -1.90, 0.12$, $SD_s = 0.97, 0.49$), $t_s(151) = 0.75, 1.73$, $p_s = .456, .085$, respectively, although these differences were not statistically significant. Entering study as a between-participants factor in each of the above analyses yielded no significant interactions, $p_s > .6$, which indicates that the results were similar across experiments. Thus, these findings illustrate that acetaminophen blunted participants' evaluations toward both unpleasant and pleasant stimuli, and this effect was most pronounced for stimuli that were the most extreme in either a negative or positive direction.

Emotional arousal

For emotional arousal, we first submitted participants' overall emotional arousal to all stimuli across the two studies to an independent-samples t test, with treatment as the

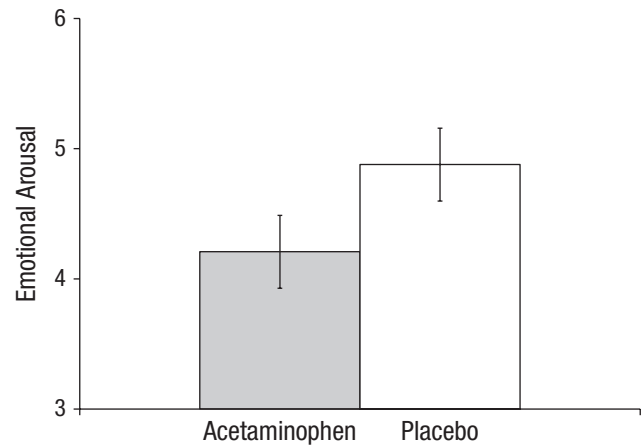


Fig. 4. Mean rating of emotional arousal toward all stimuli across studies as a function of treatment condition. Error bars represent 95% confidence intervals.

between-participants factor. As expected, participants who took acetaminophen were overall less emotionally aroused by the stimuli ($M = 4.21$, $SD = 1.23$) than participants who received a placebo ($M = 4.88$, $SD = 1.29$), $t(151) = 3.28$, $p = .001$, $\eta_p^2 = .067$ (Fig. 4).

Next, we submitted participants' emotional arousal to the stimuli across studies as categorized by their neutral, moderate, or extreme normative ratings to a 2 (treatment: acetaminophen, placebo) \times 3 (image category: neutral, moderate, or extreme) mixed-model ANOVA, with treatment as a between-participants factor and image category as a within-participants factor. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 57.41$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = 0.77$). A main effect of image category was found, $F(1.5, 232.5) = 856.60$, $p < .001$, $\eta_p^2 = .850$. Specifically, participants were least emotionally aroused by neutral stimuli, were relatively more emotionally aroused by moderately pleasant and unpleasant stimuli, and were most emotionally aroused by extremely pleasant and extremely unpleasant stimuli, which reflected normative ratings of the stimuli.

As expected, however, this analysis yielded a significant main effect of treatment, $F(1, 151) = 9.18$, $p = .003$, $\eta_p^2 = .057$, and a significant interaction of treatment and image category, $F(1.5, 232.5) = 4.08$, $p = .027$, $\eta_p^2 = .026$ (Fig. 5). Contrast analyses within each category of stimuli revealed that participants who took acetaminophen were significantly less emotionally aroused by extreme stimuli ($M = 5.85$, $SD = 1.67$) than were participants who received a placebo ($M = 6.76$, $SD = 1.53$), $t(151) = 3.52$, $p = .001$. Likewise, participants who took acetaminophen were significantly less emotionally aroused by moderate stimuli ($M = 3.83$, $SD = 1.53$) relative to participants who received a placebo ($M = 4.44$, $SD = 1.57$), $t(151) = 2.43$, $p = .016$. Participants'

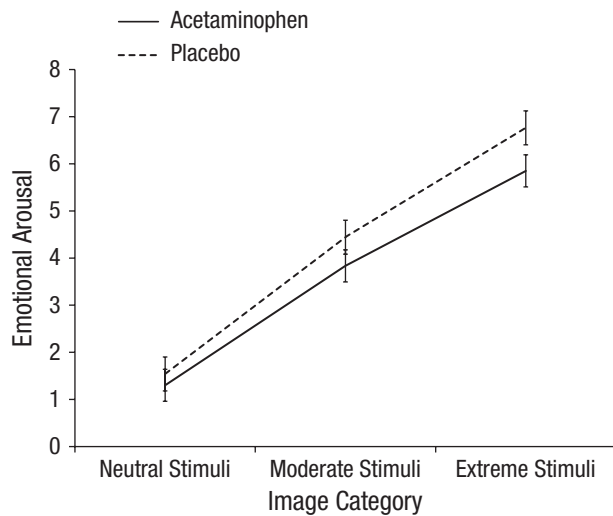


Fig. 5. Mean rating of emotional arousal toward stimuli across studies as a function of image category (collapsed across valence) and treatment condition. Error bars represent 95% confidence intervals.

emotional arousal toward neutral stimuli did not differ as a function of treatment, $p = .224$.

Finally, we submitted participants' emotional-arousal ratings within each of the five normative categories across studies to the same 2×5 mixed-model ANOVA used to analyze their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 101.64$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.72$). A main effect of normative rating was obtained, $F(2.9, 436.7) = 489.47$, $p < .001$, $\eta_p^2 = .764$. Specifically, participants expressed higher emotional arousal toward stimuli that were normatively more extreme in valence in a quadratic fashion, with the highest arousal toward extremely unpleasant and extremely pleasant stimuli, and the lowest arousal toward neutral stimuli.

As expected, however, a significant main effect of treatment was obtained, $F(1, 151) = 9.80$, $p = .002$, $\eta_p^2 = .061$, as was the predicted interaction, $F(2.9, 436.7) = 2.67$, $p = .049$, $\eta_p^2 = .017$ (Fig. 6). Contrast analyses indicated that participants who took acetaminophen were significantly less emotionally aroused by extremely pleasant stimuli ($M = 4.89$, $SD = 1.84$) than were participants who took a placebo ($M = 6.04$, $SD = 1.60$), $t(151) = 4.10$, $p < .001$. Similarly, participants who received acetaminophen were significantly less emotionally aroused by extremely unpleasant stimuli ($M = 6.81$, $SD = 1.91$) and moderately unpleasant stimuli ($M = 4.88$, $SD = 1.83$) than were participants assigned to the placebo condition ($M_s = 7.49, 6.42$, $SD_s = 1.91, 1.96$), $t_s(151) = 2.20, 1.77$, $p_s = .030, .078$, respectively. Furthermore, participants who took acetaminophen were significantly less emotionally aroused by moderately pleasant stimuli ($M = 2.79$, $SD = 1.71$) than participants who took a placebo

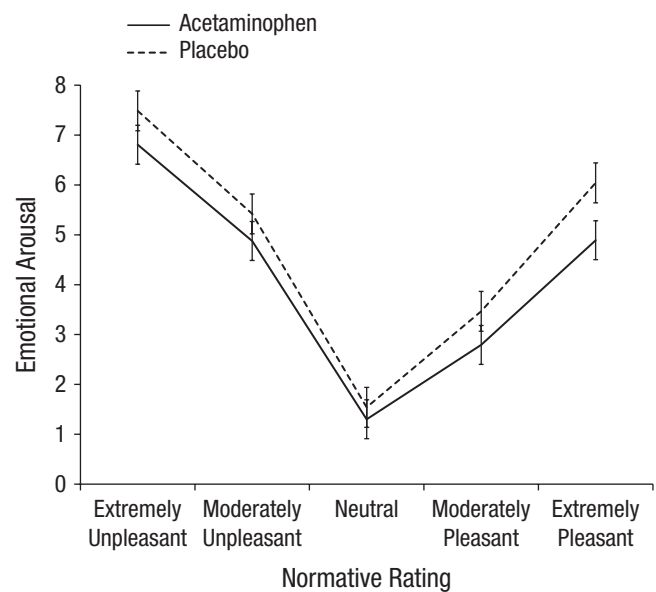


Fig. 6. Mean rating of emotional arousal toward stimuli across studies as a function of normative-rating category and treatment condition. Error bars represent 95% confidence intervals.

($M = 3.47$, $SD = 1.66$), $t(151) = 2.46$, $p = .015$. Participants did not differ in their emotional arousal toward neutral stimuli as a function of treatment, $p = .224$. Entering study as a between-participants factor in each of the analyses on emotional arousal yielded no significant interactions, $p_s > .17$, which indicates that the results were similar across experiments. In all, compared with a placebo, acetaminophen attenuated participants' emotional reactivity in general, and it did so more potently for participants' emotional reactions toward stimuli that were increasingly extreme, regardless of their negative or positive valence.

Nonevaluative judgments (ratings of color saturation)

Finally, to test whether acetaminophen specifically affected evaluative judgments or whether its effects generalize to any and all judgments of magnitude, we analyzed participants' ratings of how much the color blue was represented in each image (Study 2). To mirror the analytical approach for the other ratings, we computed an objective measure of how much blue was represented in each image akin to the normative ratings of valence and arousal of the images. For each image, we computed the average red, green, and blue levels (i.e., primary colors in the digital color space) across all pixels. Images were divided into five categories by computing the quintiles for levels of the blue component.

We first submitted participants' overall blue ratings to all stimuli to an independent-samples t test, with treatment as the between-participants factor. This analysis

yielded a nonsignificant result, $t(77) = 0.33$, $p = .744$. Specifically, participants who took acetaminophen did not significantly differ in their blueness ratings of stimuli overall ($M = 3.45$, $SD = 0.98$) compared with participants who received a placebo ($M = 3.38$, $SD = 0.83$).

We further submitted participants' blue ratings across the five levels of the images' blue content to a 2 (treatment: acetaminophen, placebo) \times 5 (objective blue content: bottom quintile, second quintile, third quintile, fourth quintile, top quintile) mixed-model ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 40.28$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = 0.82$). Objective blue content was a significant predictor of participants' blue ratings, $F(3.1, 253.7) = 269.05$, $p < .001$, $\eta_p^2 = .777$. Specifically, images in the top quintile of objective blue content were perceived to contain more blue than images in the bottom quintile, with the middle quintiles following in linear fashion, which reflected prior computations of objective color content.

However, there was no effect of treatment, $F(1, 77) = 0.11$, $p = .744$, $\eta_p^2 = .001$, and no interaction of treatment and objective blue content, $F(3.1, 253.7) = 0.11$, $p = .955$, $\eta_p^2 = .001$. Contrast analyses corroborated these findings, revealing that treatment did not significantly affect judgments of color saturation within any individual quintile, $p_s > .7$. Thus, we obtained no evidence that the effects of acetaminophen generalize beyond judgments specific to evaluative processes.

Discussion

Across two studies, we demonstrated that acetaminophen attenuates individuals' evaluations and emotional reactions to negative and positive stimuli alike. These results build on recent psychological research illustrating that acetaminophen can blunt the intensity with which individuals experience negative events that originate from physical, social, or cognitive sources (DeWall et al., 2015; DeWall et al., 2010; Randles et al., 2013). Further, these findings expand on the research to date to show that acetaminophen blunts positive evaluations in like fashion. Critically, this observed effect of acetaminophen was unique to judgments of valence and their related degree of emotional arousal, as the effect did not appear for other nonevaluative judgments of magnitude toward the same stimuli. In all, rather than being labeled as merely a pain reliever, acetaminophen might be better described as an all-purpose emotion reliever.

These effects of acetaminophen on evaluations of both negative and positive stimuli indicate that the neurochemical changes elicited by acetaminophen affect one or more related psychological evaluative processes. This mechanism of reducing valence sensitivity may be

relevant for the theory of differential susceptibility (Belsky & Pluess, 2009), which is built on the premise that a common factor (e.g., genetic variation) affects reactivity to both negative and positive events. For example, individuals with one form of a gene (short/short serotonin-transporter-linked polymorphic region, or 5-HTTLPR, genotype) had the highest levels of depressive symptomatology when experiencing negative life events but also the lowest depressive symptomatology when experiencing positive life events. For individuals with another form of the gene (long/long genotype), life events had little relationship to depressive symptomatology (Taylor et al., 2006). Such differential-susceptibility effects of the 5-HTTLPR genotype have been supported by a recent meta-analysis (van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

The effects of the 5-HTTLPR genotype are thought to be due to effects on serotonergic neurotransmission (Lesch et al., 1996; Way & Taylor, 2010). Notably, acetaminophen also affects serotonin signaling in the brain, which is necessary for the analgesic effects of the drug (Pini et al., 1996). Because acetaminophen and 5-HTTLPR both apparently affect serotonin signaling, they may be influencing a common neurochemical-psychological process that influences individuals' evaluations more broadly. In other words, the blunting effect of acetaminophen on evaluations of both negative and positive stimuli may lead to psychological reactions akin to those expected for individuals with the 5-HTTLPR long/long genotype. This suggests that modulation of the extremity of evaluation is a possible psychological mechanism that gives rise to differential susceptibility. If so, these findings suggest that the neurochemical substrates contributing to differential susceptibility can be experimentally manipulated in the laboratory. Future research will be needed to determine whether serotonergic signaling or some other neurochemical process, such as inflammatory signaling (Graham et al., 2013), is responsible for reducing evaluation extremity.

These findings additionally advance understanding of the psychological process of evaluation. Whether forming attitudes, pursuing goals, or experiencing emotions, people are constantly evaluating themselves, others, and their environment in degrees of negativity, positivity, or both. That a drug purported to relieve negative evaluations of pain also reduces positive evaluations of pleasant stimuli suggests the existence of a common evaluative psychological process that influences a wide range of thoughts and behaviors. This might mean, for instance, that certain methods designed to specifically alter individuals' reactivity to negative stimuli (e.g., treatment of phobias) could, if too broadly applied, potentially change their sensitivity to emotionally evocative stimuli more generally, including positive events (e.g., causing them to

feel less joy at a wedding). It is interesting that such diminished evaluation sensitivity could also presumably cause people to feel less conflicted, indecisive, or uncomfortable when they experience ambivalence toward individuals or experiences that elicit both negative and positive reactions (e.g., Priester & Petty, 1996; Rydell & Durso, 2012). Identifying the stage in evaluative processing that acetaminophen is affecting will be an important area for investigation in order to determine whether acetaminophen is altering evaluative processing itself or the perceived inputs or outputs to this process.

Some limitations of our work should be noted. Specifically, we cannot ascertain from the current studies whether acetaminophen might blunt individuals' attention or motivation to process emotionally evocative stimuli instead of (or in addition to) their evaluative processing of these stimuli. Future research might shed more light on whether acetaminophen also alters attentional or motivational mechanisms related to the processing of valenced stimuli, as noted in previous studies of acetaminophen and evaluation (Randles et al., 2013).

In all, it is apparent that using acetaminophen for the treatment of pain might have broader consequences than previously thought. These findings call for additional research at both psychological and neurochemical levels to expand on and better understand the mechanisms through which acetaminophen influences evaluation. Acetaminophen and other pharmacological treatments are likely to be valuable tools for understanding the basic mechanisms of evaluation and emotional reactivity, which are critical for many aspects of life studied across the different fields of psychology.

Author Contributions

G. R. O. Durso developed the study concept. All authors contributed to the study design. Data were collected and analyzed by G. R. O. Durso and A. Luttrell. G. R. O. Durso drafted the manuscript, and A. Luttrell and B. M. Way provided critical revisions. All authors approved the final version of the manuscript for submission.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

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

Open Practices

The consent form completed by participants in these studies stated, "Only the investigators and their research assistants will have access to the original research data." As a consequence, we cannot share the original data publicly at this time. However, for anyone interested in accessing the data, we would gladly add you as a co-investigator to our current research protocol. The complete Open Practices Disclosure for this article can be found at <http://pss.sagepub.com/content/by/supplemental-data>.

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**Over-the-Counter Relief from Pains and Pleasures Alike:
Acetaminophen Blunts Evaluation Sensitivity to Both Negative and Positive Stimuli**

Supplementary Materials
2014-12-29

Study 1 Results

Evaluations

On evaluations, participants' overall evaluation extremity to all stimuli in Study 1 was submitted to an independent-samples *t*-test, with treatment as the between-participants factor. As expected, participants taking acetaminophen reported overall less extreme evaluations ($M = 1.99$, $SD = 0.49$) than participants receiving placebo ($M = 2.26$, $SD = 0.52$), $t(72) = 2.25$, $p = .027$, $\eta_p^2 = .066$.

Next, we accounted for differences between stimulus categories by submitting participants' evaluation extremity to a 2 [Treatment: acetaminophen, placebo] x 3 [Normative Rating: neutral, moderate, or extreme image] mixed-model ANOVA, with treatment as between-participants and normative rating as within-participants factors. Mauchly's test indicated that the assumption of sphericity had not been violated, $\chi^2(2) = 4.03$, $p = .122$, so sphericity was assumed. A main effect of category was found, $F(2, 144) = 639.91$, $p < .001$, $\eta_p^2 = .899$, such that participants rated neutral stimuli least extremely (in either a positive or negative direction), moderate stimuli relatively more extremely than neutral stimuli, and extreme stimuli relatively more extremely than moderate stimuli, reflecting normative ratings.

As expected, however, this analysis yielded a main effect of treatment, $F(1, 72) = 4.79$, $p = .032$, $\eta_p^2 = .062$, and the predicted interaction pattern of treatment by category, $F(2, 144) = 2.07$, $p = .129$, $\eta_p^2 = .028$, although the interaction was not significant in this study. Contrast analyses within each category revealed that participants taking acetaminophen evaluated extreme stimuli ($M = 3.08$, $SD = 0.73$) significantly less extremely (in either a positive or negative direction) than did participants receiving placebo ($M = 3.45$, $SD = 0.76$), $t(72) = 2.12$, $p = .037$. Likewise, participants taking acetaminophen evaluated moderate stimuli ($M = 1.51$, $SD = 0.67$) marginally significantly less extremely than participants receiving placebo ($M = 1.79$, $SD = 0.62$), $t(72) = 1.86$, $p = .067$. Evaluation extremity toward neutral stimuli did not differ as a function of treatment, $p = .600$.

Finally, participants' raw evaluations were submitted to a 2 [Treatment: acetaminophen, placebo] x 5 [Normative Rating: extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant] mixed-model ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 61.91$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity since the epsilon value was less than or equal to 0.75 ($\epsilon = 0.67$). A main effect of category was found, $F(2.8, 202.6) = 669.43$, $p < .001$, $\eta_p^2 = .903$, such that participants rated extremely unpleasant pictures more negatively and extremely pleasant pictures more positively in a linear fashion, reflecting normative ratings. There was no main effect of treatment on evaluations, $F(1, 72) = 0.49$, $p = .487$, $\eta_p^2 = .007$, indicating that participants taking acetaminophen did not evaluate stimuli overall in either a relatively more negative or more positive direction.

These effects were qualified by a significant interaction of treatment by category, $F(2.8, 202.6) = 2.71$, $p = .050$, $\eta_p^2 = .036$, as hypothesized. Contrast analyses revealed that participants taking acetaminophen tended to rate extremely unpleasant stimuli ($M = -3.41$, $SD = 0.84$) less negatively than participants receiving placebo ($M = -3.73$, $SD = 0.83$), $t(72) = 1.63$, $p = .107$.

Likewise, participants taking acetaminophen rated extremely pleasant stimuli ($M = +2.75$, $SD = 0.93$) significantly less positively than participants receiving placebo ($M = +3.17$, $SD = 0.91$), $t(72) = 1.95$, $p = .055$.

Participants taking acetaminophen also rated moderately pleasant stimuli ($M = +1.34$, $SD = 0.96$) marginally significantly less positively than participants receiving placebo ($M = +1.73$, $SD = 0.94$), $t(72) = 1.75$, $p = .085$. Finally, participants taking acetaminophen additionally tended to rate moderately unpleasant stimuli less negatively ($M = -1.59$, $SD = 0.98$) than participants taking placebo ($M = -1.74$, $SD = 0.99$), although this difference was not significant in this study, $t(72) = 0.68$, $p = .501$. Evaluations of neutral stimuli did not differ as a function of treatment, $t(72) = 0.15$, $p = .878$.

Emotional Arousal

On emotional arousal, we first submitted participants' overall emotional arousal to all stimuli in Study 1 to an independent-samples t -test, with treatment as the between-participants factor. As expected, participants taking acetaminophen were tending overall to be less emotionally aroused by the stimuli ($M = 4.32$, $SD = 1.12$) than participants receiving placebo ($M = 4.70$, $SD = 1.24$), $t(72) = 1.39$, $p = .169$, $\eta_p^2 = .026$, although in this study this difference was not statistically significant.

Next, we submitted participants' emotional arousal to the stimuli as categorized by their neutral, moderate, or extreme normative ratings to a 2 [Treatment: acetaminophen, placebo] \times 3 [Normative Rating: neutral, moderate, or extreme] mixed-model ANOVA, with treatment as between-participants and normative rating as within-participants factors. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 16.55$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.83$). A main effect of category was found, $F(1.7, 119.2) = 457.67$, $p < .001$, $\eta_p^2 = .864$, such that participants were least emotionally aroused by neutral stimuli, were relatively more emotionally aroused by moderately pleasant and unpleasant stimuli, and were most emotionally aroused by extremely pleasant and extremely unpleasant stimuli, reflecting normative ratings.

As expected, however, this analysis yielded a main effect of differences in arousal due to treatment, $F(1, 72) = 1.60$, $p = .211$, $\eta_p^2 = .022$ (although it was not statistically significant in this study), and these effects were qualified by the predicted (though marginally significant) interaction of treatment by category, $F(1.7, 119.2) = 2.49$, $p = .095$, $\eta_p^2 = .033$. Contrast analyses within each category of stimuli revealed that participants taking acetaminophen tended to be less emotionally aroused by extreme stimuli ($M = 5.94$, $SD = 1.33$) than were participants receiving placebo ($M = 6.43$, $SD = 1.42$), $t(72) = 1.55$, $p = .125$, although this difference was not statistically significant in this study. Likewise, participants taking acetaminophen were less emotionally aroused by moderate stimuli ($M = 3.79$, $SD = 1.37$) relative to participants receiving placebo ($M = 4.37$, $SD = 1.72$), $t(72) = 1.61$, $p = .112$, although this difference was again not statistically significant in this study. Participants' emotional arousal toward neutral stimuli did not significantly differ as a function of treatment, $p = .871$.

Finally, we submitted participants' emotional arousal ratings within each of the five normative categories across studies to the same 2 \times 5 mixed-model ANOVA as with their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 28.14$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.83$). A main effect of stimulus category was obtained, $F(3.3, 240.3) = 249.72$, $p < .001$, $\eta_p^2 = .776$, such that participants expressed higher emotional arousal toward stimuli that

were normatively more extreme in valence in a quadratic fashion, with the highest arousal toward extremely unpleasant and extremely pleasant stimuli, and the lowest arousal toward neutral stimuli.

As expected, however, a main effect of treatment (though not significantly significant in this study) was obtained, $F(1,72) = 2.15, p = .147, \eta_p^2 = .029$, as was the predicted interaction (although it was not statistically significant in this study), $F(3.3, 240.3) = 1.15, p = .330, \eta_p^2 = .016$. Contrast analyses indicated that participants taking acetaminophen were marginally significantly less emotionally aroused by extremely pleasant stimuli ($M = 5.01, SD = 1.75$) than were participants taking placebo ($M = 5.65, SD = 1.55$), $t(72) = 1.67, p = .099$. Similarly, participants receiving acetaminophen were less emotionally aroused by extremely unpleasant stimuli ($M = 6.88, SD = 1.25$) than were participants assigned the placebo condition ($M = 7.23, SD = 1.84$), although this difference was not statistically significant in this study, $t(72) = 0.96, p = .341$. Furthermore, participants taking acetaminophen tended to be less emotionally aroused by moderately pleasant stimuli ($M = 2.91, SD = 1.64$) than participants taking placebo ($M = 3.49, SD = 1.89$), $t(72) = 1.44, p = .155$, and participants taking acetaminophen also tended to be less emotionally aroused by moderated unpleasant stimuli ($M = 4.68, SD = 1.42$) than participants taking placebo ($M = 5.25, SD = 2.02$), $t(72) = 1.42, p = .161$, although these differences were not statistically significant in this study. Participants did not differ significantly in their emotional arousal toward neutral stimuli as a function of treatment, $p = .871$.

Study 2 Results

Evaluations

On evaluations, participants' overall evaluation extremity to all stimuli in Study 2 was submitted to an independent-samples *t*-test, with treatment as the between-participants factor. As expected, participants taking acetaminophen reported overall less extreme evaluations ($M = 1.93, SD = 0.62$) than participants receiving placebo ($M = 2.24, SD = 0.47$), $t(77) = 2.51, p = .014, \eta_p^2 = .075$.

Next, we accounted for differences between stimulus categories by submitting participants' evaluation extremity to a 2 [Treatment: acetaminophen, placebo] x 3 [Normative Rating: neutral, moderate, or extreme image] mixed-model ANOVA, with treatment as between-participants and normative rating as within-participants factors. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 15.22, p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.85$). A main effect of category was found, $F(1.7, 130.3) = 516.80, p < .001, \eta_p^2 = .870$, such that participants rated neutral stimuli least extremely (in either a positive or negative direction), moderate stimuli relatively more extremely than neutral stimuli, and extreme stimuli relatively more extremely than moderate stimuli, reflecting normative ratings.

As expected, however, this analysis yielded a main effect of treatment, $F(1,77) = 5.45, p = .022, \eta_p^2 = .066$, and the predicted interaction of treatment by category, $F(1.7, 130.3) = 3.49, p = .041, \eta_p^2 = .043$. Contrast analyses within each category revealed that participants taking acetaminophen evaluated extreme stimuli ($M = 2.95, SD = 1.01$) significantly less extremely (in either a positive or negative direction) than did participants receiving placebo ($M = 3.46, SD = 0.67$), $t(77) = 2.60, p = .011$. Likewise, participants taking acetaminophen tended to evaluate moderate stimuli ($M = 1.55, SD = 0.70$) less extremely than participants receiving placebo ($M = 1.73, SD = 0.63$), although this difference was not statistically significant in this study, $t(77) =$

1.23, $p = .223$. Evaluation extremity toward neutral stimuli did not differ as a function of treatment, $p = .558$.

Finally, participants' raw evaluations were submitted to a 2 [Treatment: acetaminophen, placebo] x 5 [Normative Rating: extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant] mixed-model ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 134.54$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity since the epsilon value was less than or equal to 0.75 ($\epsilon=0.51$). A main effect of category was found, $F(2.0, 157.2) = 629.92$, $p < .001$, $\eta_p^2 = .891$, such that participants rated extremely unpleasant pictures more negatively and extremely pleasant pictures more positively in a linear fashion, reflecting normative ratings. There was an unexpectedly marginal main effect of treatment on evaluations, $F(1,77) = 3.69$, $p = .058$, $\eta_p^2 = .046$, such that participants taking acetaminophen evaluated stimuli overall relatively more negatively ($M = -0.32$) than participants taking placebo ($M = -0.17$).

These effects were qualified by a significant interaction of treatment by category, $F(2.0, 157.2) = 3.77$, $p = .024$, $\eta_p^2 = .047$, as hypothesized. Contrast analyses revealed that participants taking acetaminophen tended to rate extremely unpleasant stimuli ($M = -3.39$, $SD = 1.14$) less negatively than participants receiving placebo ($M = -3.74$, $SD = 0.74$), $t(77) = 1.60$, $p = .115$, though this contrast was not itself statistically significant within this study. Participants taking acetaminophen also rated extremely pleasant stimuli ($M = +2.51$, $SD = 1.07$) significantly less positively than participants receiving placebo ($M = +3.19$, $SD = 0.88$), $t(77) = 3.06$, $p = .003$.

Participants taking acetaminophen also tended to evaluate moderately pleasant stimuli ($M = +1.15$, $SD = 0.91$) less positively than participants receiving placebo ($M = +1.42$, $SD = 0.89$), $t(77) = 1.30$, $p = .198$, although this difference was not statistically significant in this study. Finally, participants taking acetaminophen tended to rate moderately unpleasant stimuli less negatively ($M = -1.84$, $SD = 0.99$) than participants taking placebo ($M = -1.93$, $SD = 0.95$), although this difference was not significant in this study, $t(77) = 0.42$, $p = .678$. Evaluations of neutral stimuli surprisingly differed as a function of treatment, $t(77) = 2.94$, $p = .004$, such that participants taking acetaminophen evaluated these stimuli significantly less positively ($M = -0.05$, $SD = 0.42$) than did participants taking placebo ($M = +0.22$, $SD = 0.38$).

Emotional Arousal

On emotional arousal, we first submitted participants' overall emotional arousal to all stimuli to an independent-samples t -test, with treatment as the between-participants factor. As expected, participants taking acetaminophen were overall significantly less emotionally aroused by the stimuli ($M = 4.10$, $SD = 1.42$) than participants receiving placebo ($M = 5.05$, $SD = 1.21$), $t(77) = 3.14$, $p = .002$, $\eta_p^2 = .114$.

Next, we submitted participants' emotional arousal to the stimuli as categorized by their neutral, moderate, or extreme normative ratings to a 2 [Treatment: acetaminophen, placebo] x 3 [Normative Rating: neutral, moderate, or extreme] mixed-model ANOVA, with treatment as between-participants and normative rating as within-participants factors. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 41.14$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon=0.72$). A main effect of category was found, $F(1.4, 111.5) = 425.69$, $p < .001$, $\eta_p^2 = .847$, such that participants were least emotionally aroused by neutral stimuli, were relatively more emotionally aroused by moderately pleasant and unpleasant stimuli, and were most emotionally aroused by extremely pleasant and extremely unpleasant stimuli, reflecting normative ratings.

As expected, however, this analysis yielded a significant main effect of treatment, $F(1,77) = 8.70, p = .004, \eta_p^2 = .102$, and the predicted interaction of treatment by category, $F(1.4, 111.5) = 3.04, p = .068, \eta_p^2 = .038$, although this interaction was marginally significant in this study. Contrast analyses within each category of stimuli revealed that participants taking acetaminophen were significantly less emotionally aroused by extreme stimuli ($M = 5.76, SD = 1.93$) than were participants receiving placebo ($M = 7.08, SD = 1.59$), $t(77) = 3.28, p = .002$. Likewise, participants taking acetaminophen were marginally significantly less emotionally aroused by moderate stimuli ($M = 3.87, SD = 1.67$) relative to participants receiving placebo ($M = 4.51, SD = 1.44$), $t(77) = 1.81, p = .074$. Participants' emotional arousal toward neutral stimuli unexpectedly differed marginally significantly as a function of treatment, $t(77) = 1.89, p = .063$, such that participants taking acetaminophen were less emotionally aroused by these stimuli ($M = 1.02, SD = 1.32$) than were participants taking placebo ($M = 1.52, SD = 0.97$).

Finally, we submitted participants' emotional arousal ratings within each of the five normative categories across studies to the same 2x5 mixed-model ANOVA as with their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 73.7, p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = 0.69$). A main effect of stimulus category was obtained, $F(2.7, 205.7) = 247.84, p < .001, \eta_p^2 = .763$, such that participants expressed higher emotional arousal toward stimuli that were normatively more extreme in valence in a quadratic fashion, with the highest arousal toward extremely unpleasant and extremely pleasant stimuli, and the lowest arousal toward neutral stimuli.

As expected, however, a significant main effect of treatment was obtained, $F(1,77) = 8.29, p = .005, \eta_p^2 = .097$, as was the predicted interaction, $F(2.7, 205.7) = 2.46, p = .071, \eta_p^2 = .031$, although it was marginally significant in this study. Contrast analyses indicated that participants taking acetaminophen were significantly less emotionally aroused by extremely pleasant stimuli ($M = 4.79, SD = 1.93$) than were participants taking placebo ($M = 6.42, SD = 1.58$), $t(77) = 4.08, p < .001$. Similarly, participants receiving acetaminophen were significantly less emotionally aroused by extremely unpleasant stimuli ($M = 6.74, SD = 2.36$) than were participants assigned the placebo condition ($M = 7.74, SD = 1.97$), $t(77) = 2.02, p = .047$.

Furthermore, participants taking acetaminophen were significantly less emotionally aroused by moderately pleasant stimuli ($M = 2.69, SD = 1.78$) than participants taking placebo ($M = 3.44, SD = 1.44$), $t(77) = 2.03, p = .046$. Finally, participants taking acetaminophen tended to be less emotionally aroused by moderately unpleasant stimuli ($M = 5.05, SD = 2.15$) than participants taking placebo ($M = 5.58, SD = 1.92$), although this difference was not statistically significant in this study $t(77) = 1.15, p = .252$. Participants also unexpectedly differed in their emotional arousal toward neutral stimuli as a function of treatment to a marginally significant extent, $t(77) = 1.89, p = .063$, such that participants taking acetaminophen were less emotionally aroused by these stimuli ($M = 1.02, SD = 1.32$) than participants taking placebo ($M = 1.52, SD = 0.97$).

Methodological Note: Participants did not provide a DNA sample for genotyping in either study.