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

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Abstract

Acetaminophen, an effective and popular over-the-counter pain reliever (e.g., Tylenol®), has recently been shown to blunt individuals' reactivity to a range of negative stimuli beyond physical pain. Because past psychological and neuroimaging research has linked reduced sensitivity to negative reactions to similarly diminished sensitivity to positive reactions, we conducted two experiments testing whether acetaminophen might blunt individuals' evaluations and emotional experiences to both negative *and* positive stimuli alike. In each study, participants received either acetaminophen or placebo, and evaluated emotionally evocative stimuli on valence (Study 1 and 2), emotional arousal (Study 1 and 2), and non-evaluative aspects (Study 2). Results revealed that participants taking acetaminophen (versus placebo) evaluated unpleasant stimuli less negatively *and* pleasant stimuli less positively, and were less emotionally aroused overall. Conversely, non-evaluative judgments were unaffected by treatment. These findings suggest that the mechanism by which acetaminophen reduces pain may more broadly blunt individuals' evaluative and emotional processing.

[150/150w]

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When people experience aches and pains, one of the most common treatments they reach for is acetaminophen (the active ingredient in Tylenol®). Pain is a fundamentally negative, emotionally taxing experience that motivates individuals to relieve it as soon as possible (Seymour & Dolan, 2013; see Wall & Melzack, 2013), and 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 et al., 2002; McNeil Consumer HealthCare, 2002). Its popularity as a pain reliever makes sense, given its relatively fast onset (11-60 minutes) and lasting effect (1-4 hours; Anderson, 2008; McQuay et al., 2007; Pini, Sandrini, & Vitale, 1996; Smith, 2009).

However, recent evidence suggests that acetaminophen might be capable of soothing more than our bodily aches and pains. Indeed, these studies have provocatively demonstrated that acetaminophen reduces individuals' sensitivity to a range of non-physical negative experiences. When taken over the course of three weeks, for instance, acetaminophen (versus placebo) reduces individuals' reported negative reactions resulting from feeling rejected in 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 yields similar attenuating effects on individuals' negative reactions toward less figuratively "painful" experiences. Specifically, Randles, Heine, and Santos (2013) found that participants receiving an acute dose of 1000mg of acetaminophen (versus placebo) exhibited reduced negative reactions to thinking about their own mortality or toward nonsensical absurdist art. More recent findings further demonstrated that acetaminophen can similarly reduce negative reactions arising from difficult decisions (DeWall, Chester, & White, 2014).

Acetaminophen: Psychological Mechanisms of Action

This collection of observations raises a pertinent question: How can a pain reliever have a common ameliorating effect on such a wide range of negative experiences, "painful" or otherwise? One potential explanation is that acetaminophen affects the magnitude of individuals' reactivity to *any* psychologically unpleasing stimulus. Though the specific bodily sites where acetaminophen exerts its effects are still not properly understood (Anderson, 2008; Pini et al., 1996; Smith, 2009), accumulating evidence indicates that they reside within the brain (Graham, Davies, Day, Mohamudally, & Scott, 2013). Thus, acetaminophen potentially validates the mantra that "pain is a state of mind."

Consistent with this notion, acetaminophen has been found to reduce neural activity in the anterior insula and anterior cingulate during an experience of social rejection (DeWall et al., 2010). The anterior insula and cingulate form key nodes in the pain matrix and appear to be primarily responsible for the affective componant of pain (Eisenberger, 2012; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Schreckenberger et al., 2005; see Apkarian et al., 2013). For example, people with lesions in the affective pain matrix report that they continue to experience the pain, but that it no longer bothers them (Berthier, Starkstein, & Leiguarda, 1988; Corkin & Hebben, 1981; Foltz & White, 1962; Hurt & Ballantine, 1973). Moreover, lesions to the affective pain matrix seem to affect individuals' evaluations toward both negative and positive stimuli more generally (Berntson, Norman, Bechara, Bruss, Tranel, and Cacioppo, 2011).

In short, acetaminophen appears to exert its effects by altering brain activity, particularly within the affective pain matrix. As a result, and as demonstrated by recent evidence (DeWall et al., 2010; DeWall et al., 2014; Randles et al., 2013), acetaminophen seems capable of blunting the extent to which people experience a range of negative psychological reactions, be they physically painful, socially hurtful, judgmentally difficult, or generally unsettling. Furthermore, the attenuating effect of acetaminophen on insular and cingulate activity in response to a negative stimulus appears to be related to decreases in self-reported negative reactions to these unpleasant experiences. This connection between blunted psychological activity and diminished negative sensitivity invites the consideration of an intriguing possibility: Is acetaminophen more broadly blunting how individuals experience *any* emotional experience?

Acetaminophen Blunts Negative and Positive Reactions Alike?

Indeed, if acetaminophen is altering individuals' negative sensitivity to unpleasant experiences, a wealth of theories and evidence from psychological and neuroimaging research suggest that it may *also* be capable of altering their *positive* sensitivity to *pleasant* experiences by altering common psychological evaluative processes. Individual differences in "affect intensity," for example, predict the extremity to which people evaluate both negative *and* positive emotional experiences (Diener, Larsen, Levine, & Emmons, 1985; Larsen & Diener, 1987; Larsen, Diener, & Emmons, 1986; Schimmack & Diener, 1997), and people who report fewer negative life events also report having fewer positive events (Suh, Diener, & Fujita, 1996). Likewise, people who experience fewer and less extreme negative moods also report experiencing fewer and less extreme positive moods (Crawford & Henry, 2004; see also Russell & Carroll, 1999).

Related research from developmental psychology, especially differential susceptibility theory (Belsky & Pluess, 2009), suggests that people who are more or less sensitive to negative experiences are similarly more or less sensitive to positive experiences in like fashion. More specifically, in contrast with diathesis-stress models of childhood development (Monroe &

Simons, 1991), differential susceptibility theory predicts that children who are more vulnerable to failure (i.e., temperamental) within negative stressful environments might *also* be more likely to *thrive* in especially positive and nurturing environments during childhood. It follows, then, that children who are less affected by negative childhood experiences would be less responsive to positive childhood environments.

Finally, neuroimaging research has shown that negative and positive stimuli alike lead to activation of cognitive networks that are related to broader evaluative and emotional processes, including the aforementioned affective pain matrix (Britton et al., 2006; Craig, 2009; Hamann, Ely, Hoffman, & Kilts, 2002; Gu, Hof, Friston, & Fan, 2013; Jabbi, Swart, & Keysers, 2007; Knutson & Greer, 2008; Lindquist & Barrett, 2012; Pollatos, Gramann, & Schandry, 2007). An especially illustrative example of both positive and negative evaluative processes relying on a common neural area was a lesion study conducted by Berntson and colleagues (2011), wherein the authors examined how individuals with damage to the insula (versus amygdala and control regions) evaluated negative and positive images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). Their results indicated that insular damage (versus amygdala and control regions) led people to evaluate unpleasant stimuli less negatively *and pleasant* stimuli less *positively*. As a consequence, these attenuated evaluations led participants with insular lesions to feel less emotionally aroused from negative and positive stimuli alike.

This last result is especially intriguing, given that the insula seems to be a critical mechanism through which acetaminophen reduces individuals' emotional reactions toward negative stimuli (e.g., DeWall et al., 2010). But, as the extant research from a variety of areas reviewed here delineates, factors which influence individuals' sensitivity to negative reactions can also diminish their sensitivity to positive experiences via common psychological evaluative processes. Taken together, these observations suggest that, if acetaminophen blunts negative reactions by attenuating the activation of broader evaluative psychological processes through the insula, acetaminophen may be more globally blunting reactions toward any negative or positive stimulus.

Thus, although the existing research has focused on how acetaminophen attenuates individuals' reactivity to a variety of negative stimuli, we propose that this drug may more generally affect individuals' evaluations, particularly toward emotionally evocative stimuli. That is, contrary to existing assumptions, acetaminophen may actually reduce positive emotional reactions as well as negative ones. We therefore predicted that people taking acetaminophen (versus placebo) would experience blunted negative reactions to unpleasant stimuli *and* blunted positive reactions to pleasant stimuli. Our first experiment was designed as an initial test of this prediction. [1249w]

Study 1

Method. Eighty-three participants were recruited to participate in an experiment on "Tylenol® and social cognition" in exchange for course credit. Participants were randomly assigned to take an acute dose of 1000mg of acetaminophen or placebo in liquid vehicle. Experimenters and participants were unaware of participants' assignment to condition.

After a 60-minute waiting period to allow acetaminophen to enter the brain (Anderson, 2008; H.S. Smith, 2009), participants completed all relevant measures on computers within individual cubicles to evaluate 40 randomly presented pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) on two dimensions. First, participants evaluated each stimulus in a random order by responding to the question, "To what extent is this

picture positive or negative?", using an 11-point scale anchored at -5 ("extremely negative") and +5 ("extremely positive"). Then, participants saw all 40 images in a newly random order and provided ratings of their emotional arousal by responding to the question, "To what extent does this picture make you feel an emotional reaction?" using an 11-point scale where 0 = "I feel little to no emotion," and 10 = "I feel an extreme amount of emotion" (Berntson et al., 2011), among other unrelated measures. For both measures, each stimulus was present on-screen until participants indicated their responses.

IAPS stimuli were selected to sample from a variety of emotional experiences and social versus nonsocial contexts, and were grouped *a priori* into five categories based on normative evaluations (Berntson et al., 2011; Lang et al., 2008). More specifically, corresponding normative ratings on valence were used to select 10 extremely unpleasant stimuli (IAPS ID: 2205, 2683, 2730, 2800, 3301, 3530, 6350, 9040, 9300, 9571), 5 moderately unpleasant stimuli (1270, 2590, 2694, 5971, 9001), 10 neutral stimuli (1670, 2372, 2570, 5395, 5520, 7000, 7041, 7175, 7186, 7224), 5 moderately pleasant stimuli (1450, 1602, 2510, 2791, 5711), and 10 extremely pleasant stimuli (2040, 2091, 4626, 4660, 5470, 7502, 8185, 8190, 8200, 8501).

From participants' responses, we computed three measures each for their evaluations and emotional arousal. First, participants' overall evaluation extremity (distance from the scale midpoint; Abelson, 1995) and overall emotional arousal toward all 40 stimuli were computed as global average scores of their evaluation extremity and emotional arousal, respectively. Then, 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. Six participants who exhibited abnormal response patterns on evaluations or emotional arousal (e.g., rating neutral stimuli more negatively than moderately or extremely unpleasant stimuli) were excluded, leaving N=77 for final analyses. At the end of the study, participants responded whether they thought they took acetaminophen, placebo, or if they had no idea. 45% of participants indicated that they did not know. Among participants who guessed, a chi-square test of independence was performed to examine whether actual treatment predicted participants' perceived treatment. As expected, this relation was not significant, $\chi^2(1,N=46) = 2.36$, $p = .124$, such that 47% of participants guessing that they took acetaminophen were actually in the placebo condition.

Evaluations

We first submitted participants' global evaluation extremity toward all stimuli to an independent-samples *t*-test, with treatment as the between-participants factor. This analysis yielded a significant difference between treatments, $t(75) = 2.79$, $p = .007$, $\eta_p^2 = .094$. Overall, participants taking acetaminophen were significantly less extreme in their evaluations ($M = 1.93$) compared to participants receiving placebo ($M = 2.27$).

Next, we submitted participants' evaluation extremity to the stimuli as categorized by their neutral, moderate, or extreme normative rating 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, $\chi^2(2) = 7.63$, $p = .022$, so degrees

of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.91). A main effect of category was found, $F(1.8, 133.0) = 588.72$, $p < .001$, $\eta_p^2 = .887$, 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.

Critically, however, this analysis yielded a main effect of treatment, $F(1,75) = 6.74$, $p = .011$, $\eta_p^2 = .082$, and the predicted interaction of treatment by category, $F(1.8, 133.0) = 4.68$, $p = .013$, $\eta_p^2 = .059$. As with the overall extremity score analyses, participants taking acetaminophen were overall less extreme in their evaluations across categories ($M = 1.59$) compared to participants receiving placebo ($M = 1.87$). Contrast analyses within each category of stimuli revealed that participants taking acetaminophen evaluated both extreme stimuli ($M = 2.94$) and moderate stimuli ($M = 1.48$) less extremely (in either a positive or negative direction) than did participants receiving placebo (Ms = 3.48, 1.79, ps = .006, .041, respectively). Evaluation extremity toward neutral stimuli did not differ as a function of treatment, $p = .846$.

Lastly, we performed a 2 [Treatment: acetaminophen, placebo] x 5 [Normative Rating: extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant] mixed-model ANOVA on participants' raw evaluations, averaged within each category of stimuli. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 86.12$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.62). A main effect of category was found, $F(2.4, 176.8) = 561.09$, $p < .001$, $\eta_p^2 = .882$, 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, $F(1,75) = 0.43$, $p = .514$, $\eta_p^2 = .006$, indicating that treatment did not significantly change overall evaluations in any one direction.

Critically, however, the predicted interaction of treatment by category was obtained, $F(2.4, 176.8) = 5.11$, $p = .004$, $\eta_p^2 = .064$. Contrast analyses revealed that participants taking acetaminophen rated extremely unpleasant ($M = -3.25$) significantly less negatively than did participants taking placebo ($M = -3.74$, $p = .023$). And, participants taking acetaminophen rated extremely *pleasant* stimuli ($M = +2.58$) significantly *less positively* than did participants receiving placebo ($M = +3.21$, $p = .010$). Participants taking acetaminophen also tended to rate moderately unpleasant stimuli less negatively ($M = -1.49$) than participants taking placebo (Ms = -1.78, $p = .203$), and also tended to rate moderately pleasant stimuli less positively ($M = +1.23$) than participants receiving placebo ($M = +1.69$, $p = .065$), although these differences were marginally significant or trending. Neutral stimuli evaluations did not differ by treatment, $p = .850$.

Emotional Arousal

Next, we submitted participants' emotional arousal ratings to similar analyses as done with evaluations. We first submitted participants' overall emotional arousal toward all stimuli to an independent-samples *t*-test, with treatment as the between-participants factor. This analysis yielded a marginally significant difference between treatments, $t(75) = 1.62$, $p = .109$, $\eta_p^2 = .034$. Overall, participants taking acetaminophen tended to be less emotionally aroused by the stimuli ($M = 5.34$) compared to participants receiving placebo ($M = 5.77$).

Then, 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, $\chi^2(2) = 23.32$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.79). A main effect of category was found, $F(1.6, 118.1) = 379.72$, $p < .001$, $\eta_p^2 = .835$, 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 unpleasant stimuli, reflecting normative ratings. This analysis did not yield a significant main effect of treatment, $F(1,75) = 1.86$, $p = .177$, $\eta_p^2 = .024$, although it was in the expected direction. Specifically, participants taking acetaminophen tended to report lower emotional arousal overall to the stimuli ($M = 4.84$) compared to participants receiving placebo ($M = 5.20$).

Critically, however, these effects were qualified by the predicted interaction of treatment by category, $F(1.6, 118.1) = 3.85$, $p = .033$, $\eta_p^2 = .049$. Contrast analyses within each category of stimuli revealed that participants taking acetaminophen were significantly less emotionally aroused by extreme stimuli ($M = 6.86$) than were participants receiving placebo ($M = 7.48$, $p = .045$). Likewise, participants taking acetaminophen tended to express diminished emotional arousal toward moderate stimuli ($M = 4.85$) relative to participants receiving placebo ($M = 5.46$, $p = .084$), although this difference was marginally significant. Emotional arousal toward neutral stimuli did not differ as a function of treatment, $p = .616$.

Finally, we submitted participants' emotional arousal ratings within each of the five normative categories to the same 2x5 mixed-model ANOVA as with their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 41.21$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.76). A main effect of picture category was obtained, $F(3.0, 229.0) = 216.26$, $p < .001$, $\eta_p^2 = .742$, 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.

Critically, however, a marginally significant main effect of treatment was obtained, $F(1,75) = 2.83$, $p = .097$, $\eta_p^2 = .036$, as was a tendency for the predicted interaction, $F(3.0, 229.0) = 1.72$, $p = .164$, $\eta_p^2 = .022$, although it was not statistically significant. As observed in previous analyses, participants taking acetaminophen tended to report lower levels of arousal toward all stimuli ($M = 5.24$) than did participants taking placebo ($M = 5.71$). Contrast analyses indicated that participants taking acetaminophen were significantly less emotionally aroused by extremely pleasant stimuli ($M = 6.00$) than were participants taking placebo ($M = 6.74$, $p = .047$). Similarly, participants receiving acetaminophen were marginally significantly less emotionally aroused by moderately unpleasant stimuli ($M = 5.67$) than were participants assigned the placebo condition ($M = 6.33$, $p = .090$). Furthermore, participants taking acetaminophen tended to be less emotionally aroused by moderately pleasant stimuli ($M = 4.03$) and less emotionally aroused by extremely unpleasant stimuli ($M = 7.72$) than were participants taking placebo (Ms = 4.59, 8.23, ps = .173, .166, respectively), although these differences were not statistically significant. Emotional arousal toward neutral stimuli did not differ significantly as a function of treatment, $p = .616$. In all, acetaminophen (versus placebo) attenuated participants' emotional reactivity more potently toward stimuli that were increasingly extreme in valence, regardless of direction.

Discussion

These findings replicate and expand on past results showing that acetaminophen can effectively attenuate individuals' experienced negativity toward unpleasant stimuli (DeWall et

al., 2010; DeWall et al., 2014; McQuay et al., 2007; Randles et al., 2013), even when these affective experiences are merely in response to viewing relatively impersonal photographic stimuli. However, Study 1 demonstrated for the first time that acetaminophen similarly attenuates individuals' experienced *positivity* toward increasingly *pleasant* stimuli. It also was found that acetaminophen (versus placebo) broadly diminished the emotional arousal that people experienced toward the increasingly extreme stimuli, regardless of direction, although these results were statistically weaker compared to evaluations. These results provide initial support for the notion that that acetaminophen appears to reduce perceived pain because its mechanism of action works more broadly to blunt individuals' valence sensitivity to negative and positive experiences alike, rather than acting specifically on painful experiences *per se*.

What remains unclear, however, is whether these effects are truly effects of acetaminophen on *evaluative* judgments, or whether acetaminophen affects any judgment of relative magnitude (e.g., saturation, size). Furthermore, though the results on emotional arousal were promising, they were statistically weaker than those obtained for the effect acetaminophen on evaluations. In all, the specific consequences of acetaminophen on evaluation extremity, compared to other psychologically relevant outcomes, remain speculative based on Study 1.

Thus, we designed a second experiment to address these issues. First, we thought it was critical to replicate the novel finding that acetaminophen blunts evaluation extremity toward negative and positive stimuli alike. Additionally, we wanted to test for more convincing evidence that acetaminophen attenuates not just evaluation extremity, but emotional arousal as well. Finally, we sought to test whether the effects of acetaminophen on diminished evaluation extremity are due to a more global attenuation of any judgments of magnitude, or whether its effect is specific to evaluations of relative negativity and positivity. Thus, Study 2 aimed to replicate and bolster the findings of Study 1, with the additional goal of examining whether acetaminophen blunts any and all judgments of magnitude, or if its effects are specific to evaluations. [347w]

Study 2

Method. Ninety-one participants were recruited to participate in an experiment on "Tylenol® and social cognition" in exchange for course credit. Participants were randomly assigned to take an acute dose of 1000mg of acetaminophen or placebo, in liquid vehicle. Experimenters and participants were unaware of participants' assignment to condition.

The procedure and stimuli were identical to Study 1, with participants providing one additional rating of each stimulus. After indicating their evaluations of and emotional arousal toward each stimulus, participants saw all images one last time, in a newly randomized order, and indicated the extent to which each picture contained the color blue, responding for each picture to the question, "To what extent is the color blue represented in this picture?" using an 11-point scale, where 0 = "The picture has zero blue color," and 10 = "This picture is 100% the color blue." This measure was designed to have participants focus on a dimension of judgment about each picture that would be minimally influenced by evaluative aspects of each picture, in order to test whether acetaminophen affects evaluations specifically, or if it blunts any and all judgments of magnitude.

Results. 10 participants who exhibited abnormal response patterns on evaluations or emotional arousal (e.g., rating extremely unpleasant stimuli less negatively than moderately unpleasant stimuli) were excluded, leaving N=81 for final analyses. At the end of the study, participants indicated whether they thought they took acetaminophen or placebo. A chi-square

test of independence was performed to examine whether actual treatment predicted participants' perceived treatment. As expected, this relation was not significant, $\chi^2(1,N=81) = 0.08$, $p = .774$, such that 51% of participants guessing that they took acetaminophen were actually in the placebo condition.

Evaluations

As in Study 1, we computed the extent to which participants' ratings of each stimulus was distant from the scale midpoint (extremity scores), arriving at two measures: An overall measure of participants' evaluation extremity toward all 40 stimuli, as well as participants' evaluation extremity within each of the neutral, moderate (both pleasant and unpleasant), and extreme (both pleasant and unpleasant) categories of stimuli.

We first submitted participants' overall evaluation extremity to all stimuli to an independent-samples *t*-test, with treatment as the between-participants factor. This analysis yielded a significant result, $t(79) = 2.05$, $p = .043$, $\eta_p^2 = .051$, such that participants' taking acetaminophen were overall less extreme in their evaluations ($M = 1.59$) compared to participants receiving placebo ($M = 1.80$).

Next, we submitted participants' evaluation extremity to the stimuli as categorized by their neutral, moderate, or extreme normative rating 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, $\chi^2(2) = 17.74$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon=0.83$). A main effect of category was found, $F(1.7, 131.3) = 539.23$, $p < .001$, $\eta_p^2 = .872$, 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.

Critically, however, this analysis yielded the predicted main effect of treatment, $F(1,79) = 3.48$, $p = .066$, $\eta_p^2 = .042$, and the predicted interaction of treatment by category, $F(1.7, 131.3) = 3.02$, $p = .062$, $\eta_p^2 = .037$, although both effects in this study were instead marginally significant. As with the overall extremity score analyses, participants taking acetaminophen were overall less extreme in their evaluations across categories ($M = 1.64$) compared to participants receiving placebo ($M = 1.84$). Contrast analyses within each category of stimuli revealed that participants taking acetaminophen evaluated extreme stimuli ($M = 3.02$) significantly less extremely (in either a positive or negative direction) than did participants receiving placebo (Ms = 3.47, $p = .029$). Likewise, participants taking acetaminophen tended to express diminished evaluation extremity toward moderate stimuli ($M = 1.61$) relative to participants receiving placebo ($M = 1.77$, $p = .294$), although in this study this difference was not statistically different. Evaluation extremity toward neutral stimuli did not differ as a function of treatment, $p = .946$.

Finally, we performed a 2 [Treatment: acetaminophen, placebo] x 5 [Normative Rating: extremely unpleasant, moderately unpleasant, neutral, moderately pleasant, extremely pleasant] mixed-model ANOVA on participants' evaluations of IAPS stimuli from each category. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 148.16$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon=0.49$). A main effect of category was found, $F(2.0, 155.1) = 632.60$, $p < .001$, $\eta_p^2 = .883$, such that participants rated extremely unpleasant pictures more negatively and extremely pleasant pictures more positively, with other categories falling in a typical linear fashion, reflecting normative

ratings. There was no main effect of treatment on evaluations, $F(1,79) = 1.26$, $p = .265$, indicating that treatment did not significantly change overall evaluations in any one direction.

Once again, as in Study 1, these effects were qualified by the predicted interaction of treatment by category, $F(2.0, 155.1) = 2.89$, $p = .062$, $\eta_p^2 = .035$, although in this study the effect of the interaction was marginally significant. Contrast analyses revealed that participants taking acetaminophen rated extremely pleasant ($M = +2.60$) significantly less positively than did participants receiving placebo ($M = +3.18$, $p = .014$). Likewise, participants taking acetaminophen tended to rate extremely unpleasant stimuli less negatively ($M = -3.44$) than did participants receiving placebo ($M = 3.75$, $p = .139$), although this difference was not statistically significant in this study. And, participants taking acetaminophen tended to rate moderately unpleasant stimuli less negatively ($M = -1.85$) and moderately pleasant stimuli less positively ($M = +1.27$) compared to participants receiving placebo (Ms = -2.01, +1.42), although these differences were not statistically significant (ps = .458, .498, respectively). Finally, participants taking acetaminophen unexpectedly evaluated neutral stimuli significantly less positively ($M = -0.03$) than did participants receiving placebo ($M = +0.19$, $p = .018$).

Emotional Arousal

Next, we submitted participants' emotional arousal ratings to similar analyses as evaluations, as in Study 1. Specifically, we first averaged participants' emotional arousal ratings to all 40 stimuli to derive a score of participants' overall emotional arousal. Next, we averaged emotional arousal ratings within each of the neutral, moderate, and extreme categories of stimuli (collapsing across positive and negative valence, as done with evaluations). Finally, we then submitted participants' average emotional arousal ratings within each of the five categories of stimuli, as with evaluations.

We first submitted participants' overall emotional arousal to all stimuli to an independent-samples t-test, with treatment as the between-participants factor. This analysis yielded a significant result, $t(79) = 2.60$, $p = .011$, $\eta_p^2 = .079$. Participants taking acetaminophen were overall less emotionally aroused by the stimuli ($M = 4.18$) compared to participants receiving placebo ($M = 4.82$).

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, $\chi^2(2) = 43.06$, $p < .001$, so degrees of freedom were corrected using Hunyh-Feldt estimates of sphericity (ε=0.72). A main effect of category was found, $F(1.4, 113.8) = 438.09$, $p < .001$, $\eta_p^2 = .847$, such that participants were least emotionally aroused by neutral stimuli, were relatively more emotionally aroused by moderate pleasant and unpleasant stimuli, and were most emotionally aroused by extreme pleasant and unpleasant stimuli, reflecting normative ratings.

Critically, however, this analysis yielded a significant main effect of treatment, $F(1,79) = 5.78$, $p = .019$, $\eta_p^2 = .068$, and the predicted interaction of treatment by category, $F(1.4, 113.8) = 2.52$, $p = .101$, $\eta_p^2 = .031$, although the effect of the interaction was only marginally significant. As seen in the prior analyses, participants taking acetaminophen were overall less emotionally aroused across categories ($M = 4.66$) compared to participants receiving placebo ($M = 5.35$). Contrast analyses within each category of stimuli revealed that participants taking acetaminophen were significantly less emotionally aroused by extreme stimuli ($M = 6.91$) than were participants receiving placebo ($M = 8.05$, $p = .007$). Likewise, participants taking

acetaminophen tended to express less emotional arousal toward moderate stimuli (M = 5.01) relative to participants receiving placebo (M = 5.49, p = .189), although this difference was not statistically significant. Lastly, somewhat unexpectedly, participants taking acetaminophen also tended to be less emotionally aroused by neutral stimuli (M = 2.06) compared to participants receiving placebo (M = 2.50, p = .104).

We then submitted participants' emotional arousal ratings within each of the five normative categories to the same 2x5 mixed-model ANOVA as with their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 70.69$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.70). A main effect of picture category was obtained, $F(2.8, 220.6) = 245.91$, $p < .001$, $\eta_p^2 = .757$, 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.

Critically, however, a main effect of treatment was obtained, $F(1,79) = 5.47$, p = .022, η_p^2 = .065, as was a tendency for the predicted interaction, $F(2.8, 220.6) = 1.95$, p = .127, η_p^2 = .024, although it was not statistically significant. As observed in previous analyses, participants taking acetaminophen reported lower levels of arousal toward all stimuli (M = 5.18) than did participants taking placebo (M = 5.92). Contrast analyses indicated that participants taking acetaminophen were significantly less emotionally aroused by extremely pleasant stimuli (M = 5.97) than were participants taking placebo (M = 7.38, p = .001). Similarly, participants receiving acetaminophen were marginally significantly less emotionally aroused by extremely unpleasant stimuli (M = 7.84) than were participants assigned the placebo condition (M = 8.72, p = .077). Furthermore, participants taking acetaminophen tended to be less emotionally aroused by moderately pleasant stimuli (M = 3.91) and less emotionally aroused by moderately unpleasant stimuli (M = 6.11) than were participants taking placebo (Ms = 4.33, 6.65, ps = .303, .238, respectively), although these differences were not statistically significant. Finally, participants taking acetaminophen unexpectedly tended to be less emotionally aroused toward neutral stimuli (M = 2.06) than were participants taking placebo (M = 2.50), p = .104. In all, acetaminophen (versus placebo) attenuated participants' emotional reactivity more potently toward stimuli that were increasingly extreme in valence, regardless of direction.

Non-evaluative Judgments (Blue Content Ratings)

Finally, participants' ratings of how much of the color blue was represented in all of the stimuli, as well as their ratings within each of five quintiles (based on RGB-computed blue content analyses). 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 non-significant result, $t(79) = -0.25$, p = .802, η_p^2 = .001, such that participants' taking acetaminophen did not differ in their blueness ratings of stimuli overall (M = 3.42) compared to participants receiving placebo (M = 3.38).

We then submitted participants' blue ratings across the five quintiles of IAPS stimuli to a 2 [Treatment: acetaminophen, placebo] x 5 [Objective Rating: 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, $\chi^2(9) = 41.46$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.78). Objective category was a significant predictor of participants' blue ratings, $F(3.1, 247.9) = 258.56$, $p < .001$, η_p^2 = .766, indicating that participants rated these stimuli as being meaningfully different in the extent

to which the color blue was represented across quintiles, reflecting RGB-computed blue content ratings.

However, there was no effect of treatment, $F(1,79) = 0.06$, $p = .802$, $\eta_p^2 = .001$, and no interaction of treatment by category, $F(3.1, 247.9) = 0.21$, $p = .899$, $\eta_p^2 = .003$. Contrast analyses corroborated these findings, revealing that treatment did not significantly affect color saturation judgments within any individual quintile, ps > .6. Thus, these results suggest that the blunting effects of acetaminophen (versus placebo) appear to be unique to evaluative (versus non-evaluative) processes.

Combined study analyses. In accord with recommended approaches to meta-analyzing multiple studies (Eich, 2014), we combined the two studies (N=158) and submitted participants' evaluations and emotional arousal to the same three analyses that were conducted within each study.

Evaluations

On evaluations, participants' overall evaluation extremity to all stimuli was submitted to an independent-samples t-test, with treatment as the between-participants factor. This analysis yielded a significant result, $t(156) = 3.26$, $p = .001$, $\eta_p^2 = .064$ (Figure 1). Specifically, participants taking acetaminophen were overall less extreme in their evaluations ($M = 1.75$) compared to participants receiving placebo ($M = 2.03$).

Next, we submitted participants' evaluation extremity to the stimuli as categorized by their neutral, moderate, or extreme normative categories 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, $\chi^2(2) = 22.69$, $p < .001$, so degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=0.88). A main effect of category was found, $F(1.8, 274.6) = 1128.40$, $p < .001$, $\eta_p^2 = .879$, 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, $F(1,156) = 9.97$, $p = .002$, $\eta_p^2 = .060$, and the predicted interaction of treatment by category, $F(1.8, 274.6) = 7.39$, $p = .001$, $\eta_p^2 = .045$ (Figure 2). As with the overall extremity score analyses, participants taking acetaminophen were overall less extreme in their evaluations across categories ($M = 1.62$) compared to participants receiving placebo ($M = 1.86$). Contrast analyses within each category revealed that participants taking acetaminophen evaluated extreme stimuli ($M = 2.99$) significantly less extremely (in either a positive or negative direction) than did participants receiving placebo ($M = 3.47$, $p < .001$). Likewise, participants taking acetaminophen evaluated moderate stimuli ($M = 1.54$) significantly less extremely relative to participants receiving placebo ($M = 1.78$, $p = .030$). Evaluation extremity toward neutral stimuli did not differ as a function of treatment across studies, $p = .834$.

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, $\chi^2(9) = 227.68$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.54). A main effect of category was found, $F(2.2, 338.1) = 1198.03$, $p < .001$, $\eta_p^2 = .885$, 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, $F(1,156) = 1.55$, $p = .215$, $\eta_p^2 = .010$, indicating that treatment did not significantly change overall evaluations in any one direction.

Unsurprisingly, however, as shown in the past two studies, this main effect of category was qualified by a significant interaction of treatment by category, $F(2.2, 338.1) = 7.51$, $p < .001$, $\eta_p^2 = .046$ (Figure 3). Contrast analyses revealed that participants taking acetaminophen rated extremely unpleasant stimuli ($M = -3.35$) significantly less negatively than participants receiving placebo ($M = -3.75$, $p = .009$). As predicted, participants taking acetaminophen also rated extremely pleasant stimuli ($M = +2.59$) significantly less positively than participants receiving placebo ($M = 3.19$, $p < .001$). Likewise, participants taking acetaminophen tended to rate moderately pleasant stimuli ($M = +1.25$) less positively than participants receiving placebo ($M = +1.55$, $p = .067$), although this difference was only marginally significant. Finally, participants taking acetaminophen additionally tended to rate moderately unpleasant stimuli less negatively ($M = -1.68$) and neutral stimuli less positively ($M = -0.004$) compared to participants receiving placebo (Ms = -1.90, +0.12, ps = .161, .102, respectively), although these differences were not statistically significant. Thus, the results across studies 1 and 2 illustrate that aceatminophen blunted participants' evaluations toward both unpleasing and pleasing experiences, and this effect was most pronounced for stimuli that were more extreme in either a negative or positive direction.

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. This analysis yielded a significant result, $t(156) = 2.76$, $p = .006$, $\eta_p^2 = .047$ (Figure 4). Specifically, participants taking acetaminophen were overall less emotionally aroused by the stimuli ($M = 4.74$) compared to participants receiving placebo ($M = 5.29$).

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, $\chi^2(2) = 68.03$, $p < .001$, so degrees of freedom were corrected using Hunyh-Feldt estimates of sphericity (ε=0.75). A main effect of category was found, $F(1.5, 233.4) = 792.26$, $p < .001$, $\eta_p^2 = .835$, such that participants were least emotionally aroused by neutral stimuli, were relatively more emotionally aroused by moderate pleasant and unpleasant stimuli, and were most emotionally aroused by extreme pleasant and unpleasant stimuli, reflecting normative ratings.

As expected, however, this analysis yielded a significant main effect of treatment, $F(1,156) = 7.38$, $p = .007$, $\eta_p^2 = .045$, and a significant interaction of treatment by category, $F(1.5, 233.4) = 4.59$, $p = .019$, $\eta_p^2 = .029$ (Figure 5). As seen in the prior analyses, participants taking acetaminophen were overall less emotionally aroused across categories ($M = 4.75$) compared to participants receiving placebo ($M = 5.27$). Contrast analyses within each category of stimuli revealed that participants taking acetaminophen were significantly less emotionally aroused by extreme stimuli ($M = 6.88$) than were participants receiving placebo ($M = 7.77$, $p = .001$). Likewise, participants taking acetaminophen were significantly less emotionally aroused by moderate stimuli ($M = 4.93$) relative to participants receiving placebo ($M = 5.48$, $p = .032$). Participants' emotional arousal toward neutral stimuli did not differ as a function of treatment across the two studies, $p = .468$.

Finally, we submitted participants' emotional arousal ratings within each of the five normative categories to the same 2x5 mixed-model ANOVA as with their evaluations. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 112.91$, $p < .001$, so degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε=0.73). A main effect of stimulus category was obtained, $F(2.9, 441.0) = 454.45$, $p < .001$, $\eta_p^2 = .744$, 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 based on previous analyses, however, a significant main effect of treatment was obtained, $F(1,156) = 8.31$, $p = .004$, $\eta_p^2 = .051$, as was the predicted interaction, $F(2.9, 441.0) = 2.70$, $p = .047$, $\eta_p^2 = .017$ (Figure 6). As in prior analyses, participants taking acetaminophen reported lower levels of arousal toward all stimuli ($M = 5.21$) than did participants taking placebo ($M = 5.81$). Contrast analyses indicated that participants taking acetaminophen were significantly less emotionally aroused by extremely pleasant stimuli ($M = 5.98$) than were participants taking placebo ($M = 7.07$, $p < .001$). Similarly, participants receiving acetaminophen were significantly less emotionally aroused by extremely unpleasant stimuli ($M = 7.78$) and moderately unpleasant stimuli ($M = 5.90$) than were participants assigned the placebo condition (Ms = 8.47, 6.49, ps = .025, .048, respectively). Furthermore, participants taking acetaminophen marginally significantly less emotionally aroused by moderately pleasant stimuli ($M = 3.97$) than participants taking placebo ($M = 4.46$, $p = .088$). Participants did not differ in their emotional arousal toward neutral stimuli as a function of treatment across studies, $p = .468$. In all, acetaminophen (versus placebo) attenuated participants' emotional reactivity more potently toward stimuli that were increasingly extreme in valence, regardless of their negative or positive content.

Mediation model: Tylenol → Arousal → Extremity, b = -.11,
99% CI: [-.2349, -.0022]
99.9% CI: [-.3236, +.0241]
Mediation model: Tylenol → Extremity → Arousal, b = -.29,
99% CI: [-.5878, -.0747]
99.9% CI: [-.7090, -.0070]

(** Figures 1-6 around here **)

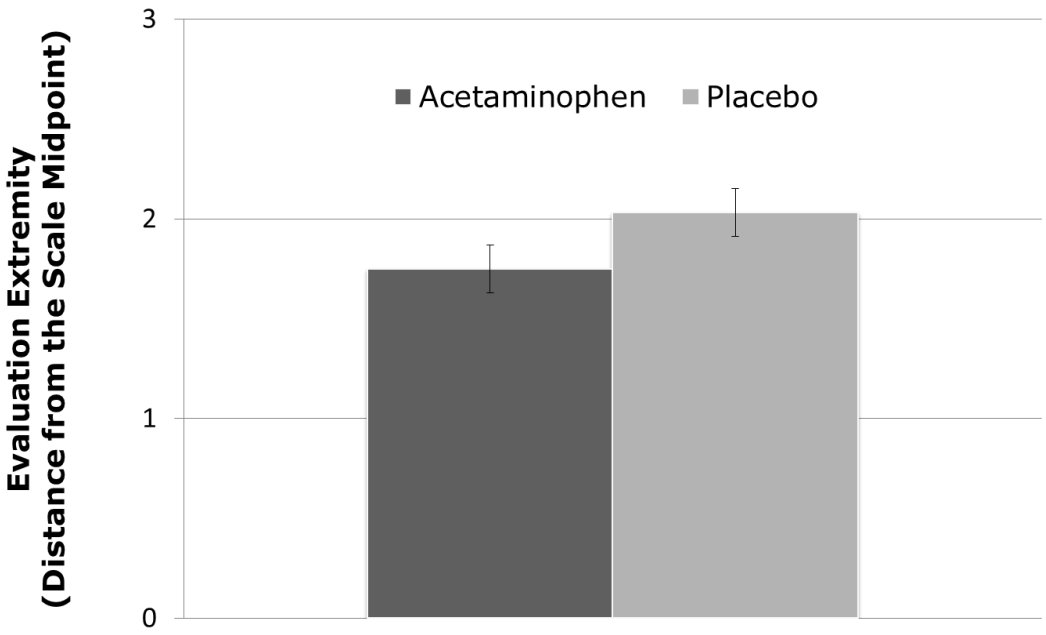

Figure 1. Effect of treatment on evaluation extremity toward all stimuli. Error bars represent 95% confidence intervals.

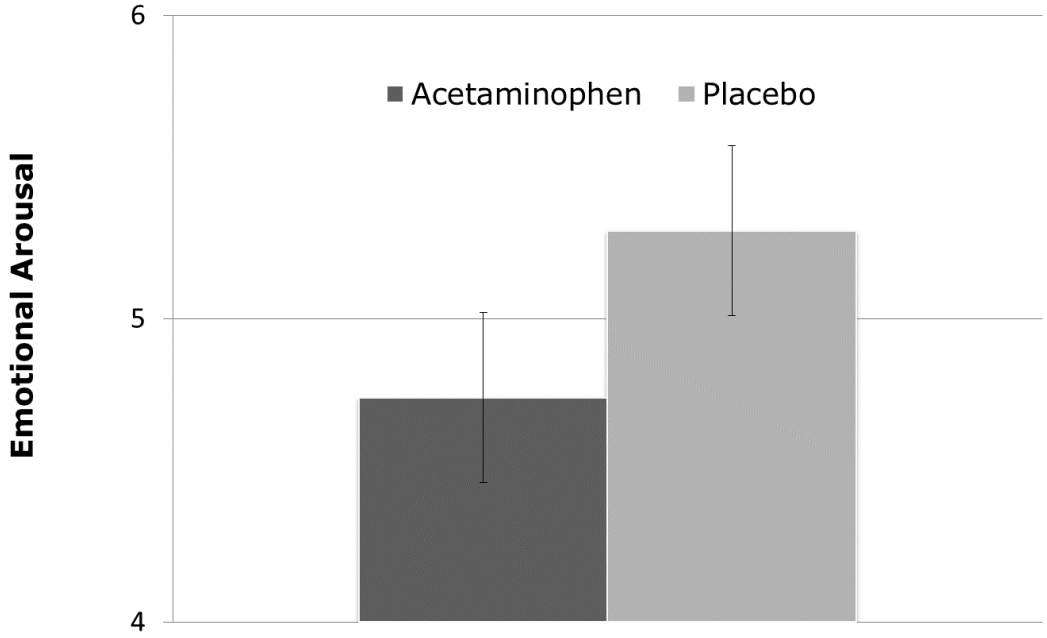

Figure 4. Effect of treatment on emotional arousal toward all stimuli. Error bars represent 95% confidence intervals.

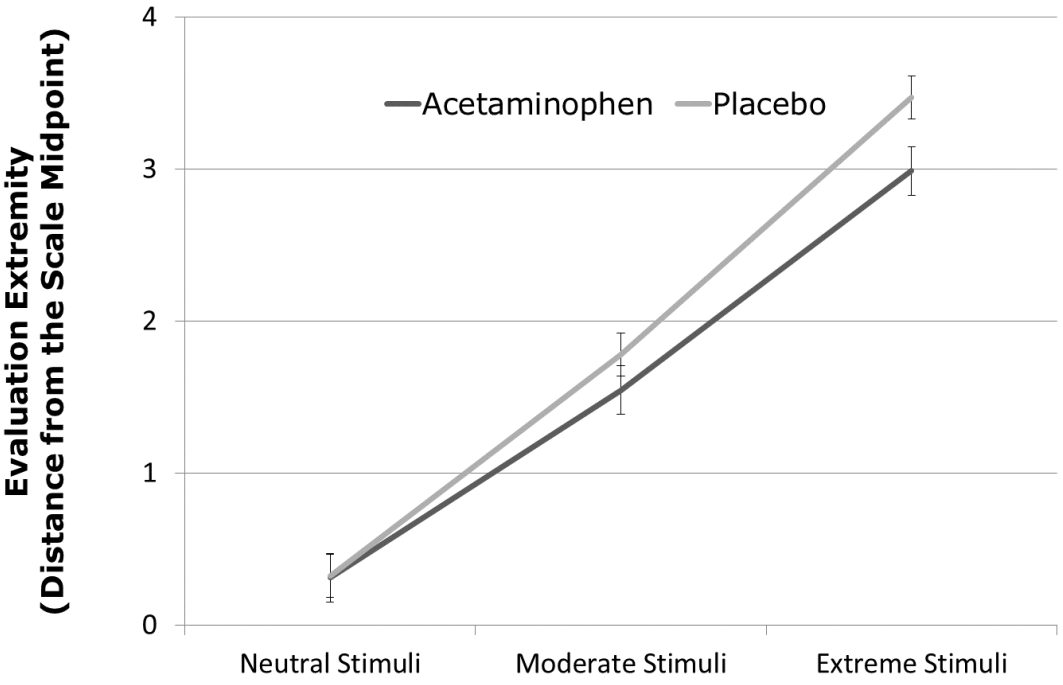

Figure 2. Effect of treatment on evaluation extremity toward neutral, moderate, and extreme stimuli. Error bars represent 95% confidence intervals.

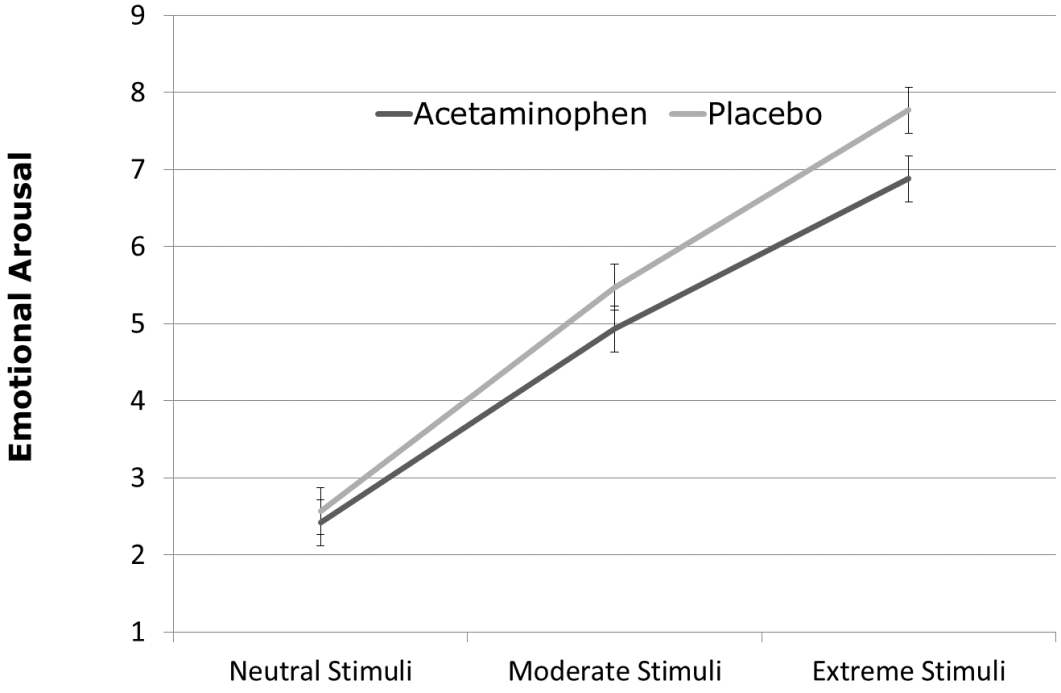

Figure 5. Effect of treatment on emotional arousal toward neutral, moderate, and extreme stimuli. Error bars represent 95% confidence intervals.

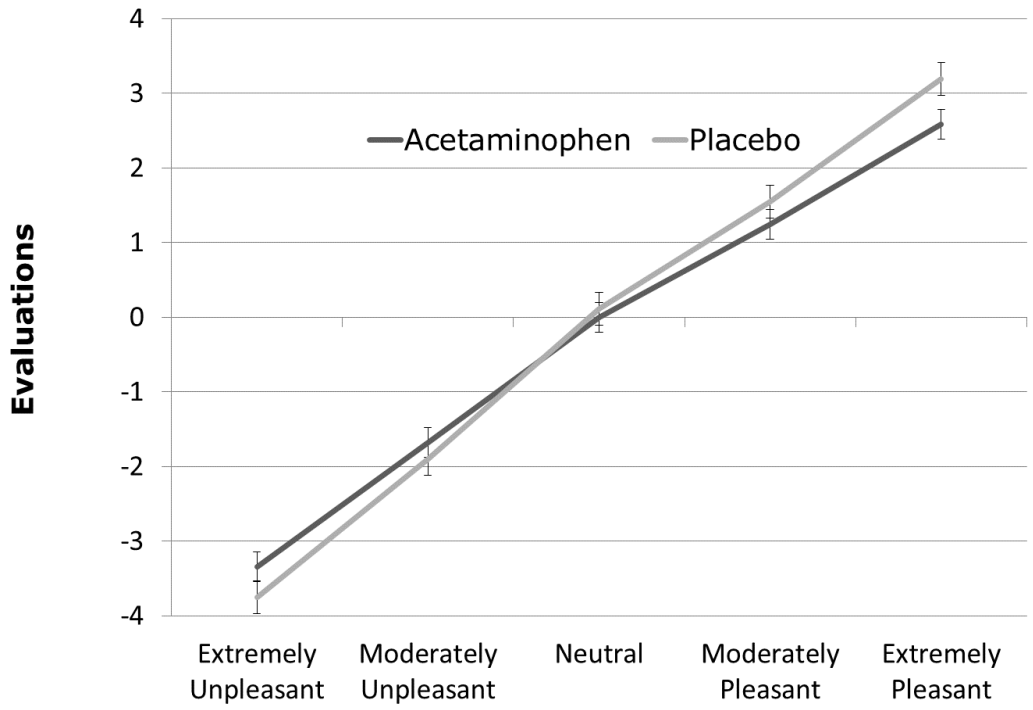

Figure 3. Effect of treatment on evaluations toward each category of stimuli. Error bars represent 95% confidence intervals.

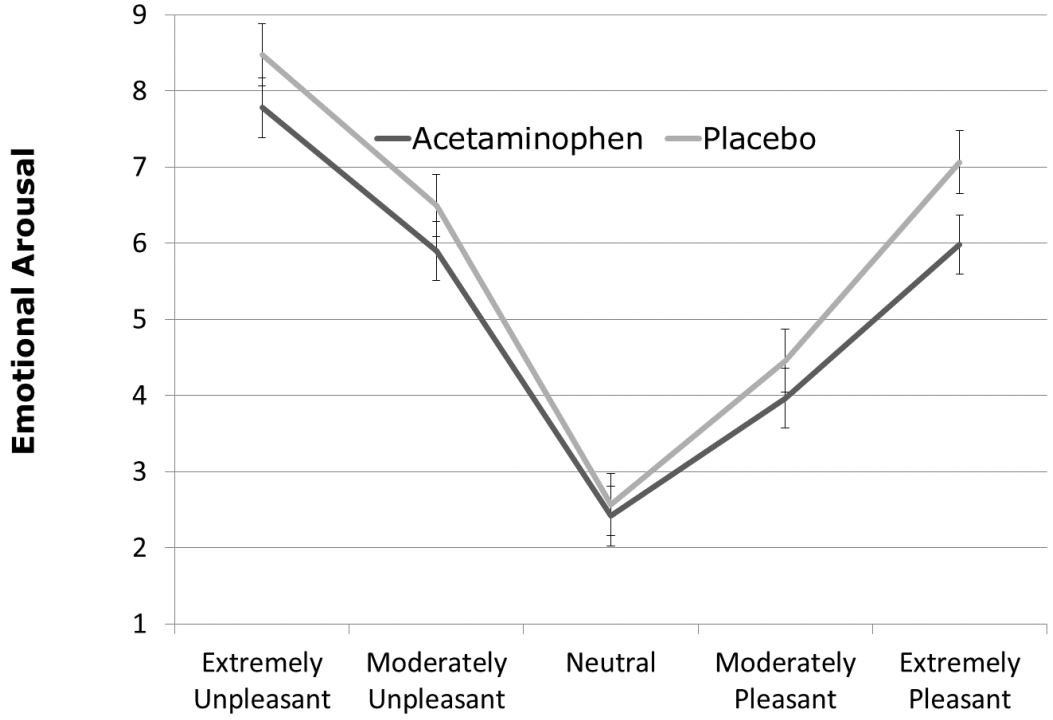

Figure 6. Effect of treatment on emotional arousal toward each category of stimuli. Error bars represent 95% confidence intervals.

General Discussion

In two studies, we demonstrated that acetaminophen desensitizes individuals' sensitivity to evaluations of negative and positive experiences alike. These results replicate and expand on past work, illustrating that acetaminophen can blunt the intensity with which individuals experience negative events that originate from physical (McQuay et al., 2007), social (DeWall et al., 2010), or cognitive sources (DeWall et al., 2014; Randles et al., 2013), even when those experiences are merely depicted pictorally. These results also extend our knowledge of the effects of acetaminophen on social perception by illustrating that its mechanism of "pain relief" might ironically diminish the *pleasure* with which people enjoy *positive* experiences as well. Critically, this observed effect of acetaminophen was unique to judgments of valence and their consequent degree of affective intensity, without affecting other non-evaluative judgments of magnitude toward the same stimuli. In other words, acetaminophen seems to relieve pain by altering how people perceive any and all emotionally-relevant information, be it negative or positive in nature. Rather than being labelled as a pain reliver, acetaminophen might be better described as an *emotion* reliever.

It seems that using acetaminophen for the treatment of pain has far broader consequences than previously thought. Given that evaluations are critical for predicting how people form attitudes and behave when navigating their immediate and future environments (Fazio, Eiser, & Shook, 2004), a better understanding of the neurochemical influences on processes related to attitude formation can inform researchers of how risk-averse *and* how reward-sensitive individuals feel when presented an opportunity to act on their differentially sensitive evaluative judgments. Such direct consequences of taking acetaminophen might include attenuated valence weighting biases toward both positive and negative information in individuals' social environments (Belsky & Pluess, 2009; Pietri, Shook, & Fazio, 2013; Rocklage & Fazio, 2014), reduced responsiveness to persuasion (Petty & Wegener, 1998), and fewer negative and positive reactions leading to diminished feelings of ambivalence (Priester & Petty, 1996).

Some limitations should be noted. Specifically, the abnormal response patterns on normative evaluations and emotional arousal ratings in both studies were unexpected. We suspect that many (if not all) of these participants were simply not taking the experiment seriously, but this remains speculative. Future studies can examine these responses with greater attention, and specifically whether these abnormal patterns reflect psychologically meaningful or unmeaningful differences between participants. It is also possible, for example, that acetaminophen not only attenuates individuals' mean-level reactions to negative and positive experiences but also affects to a lesser extent the degree to which they vary in their reactivity to these experiences. Future research on acetaminophen and its effects on cognitive and evaluative processes might better disentangle its specific mechanism, such as whether it affects relatively more automatic versus controlled processes relevant to evaluation and emotional regulation.

In sum, the potential implications of attenuated evaluation extremity and emotional arousal due to acetaminophen encompass multiple disciplines across psychological and biological sciences. There remain several interesting directions for future research on the effects of acetaminophen (among other neurochemical modulators), as highlighted above. These findings are what we hope to be representative of a larger research movement in social, developmental, and cognitive psychology that employs neurochemical measures and manipulations to study the complex relationship between our understanding of fine-grained neurochemical system regulation with a full appreciation of the depth of human experience. [546w]

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Authorship

GRO Durso developed the study concept. All authors contributed to the study design. Data were collected and analyzed by GRO Durso and A Luttrell. GRO Durso drafted the paper, and A Luttrell and BM Way provided critical revisions. All authors approved the final version of the paper for submission. 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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