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Acetaminophen Does Not Alter the Early Processing of Emotional Facial Expressions: An Eye-tracking Study

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ABSTRACT

A growing body of research has uncovered that acetaminophen, the most commonly used over-the-counter painkilling drug in the United States, produces a number of unintended psychological effects. In particular, recent studies show that acetaminophen blunts a variety of adaptive affective and cognitive processes, including our sensitivity to painful social experiences and subjective responses to emotional stimuli. Using a double-blind placebo-controlled study, here we examined whether acetaminophen alters the early visual processing of emotional facial expressions. Participants consumed 1000 mg of acetaminophen, or a matched placebo, prior to performing a delayed disengagement task with different facial expressions. Specifically, we used eye-tracking software to assess the latency to look away from neutral, happy, and angry faces. Based on prior research, we hypothesized that acetaminophen would reduce the typical delay in disengaging from emotional expressions. Our findings showed a significant main effect of facial expression, with happy faces producing the greatest delay, but there was no difference in response between the acetaminophen and placebo conditions. These results indicate that acetaminophen does not alter our initial assessment of emotional facial expressions, but we suggest further research be conducted to examine how this widely consumed drug may alter the detection and perception of emotions in others.

KEYWORDS

Acetaminophen, Delayed Disengagement, Emotional Processing, Evolutionary Mismatch, Neuromodulation, Visual Attention

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INTRODUCTION

Medicinal drugs generally offer major health and societal benefits, but they can also disrupt or inhibit mechanisms that promote adaptive fitness outcomes (Nesse & Berrdige, 1997). For example, the unpleasantness of physical pain is highly adaptive and critical for survival, as it draws our attention and serves to motivate responses to alleviate the discomfort. Therefore, the routine dulling of pain from over-the-counter (OTC) drugs and other pain medications can produce a mismatch with evolved psychological mechanisms to minimize distress (Gallup, 2019).

Acetaminophen (paracetamol, Tylenol) is the most common OTC painkiller in the United States, with estimates suggesting that nearly one in four adults consumes a medication containing acetaminophen each week (Kaufman et al., 2002). As an analgesic, acetaminophen is well tolerated and effective in reducing mild to moderate physical pain and ailments, providing relief from headaches, and reducing fever. Acetaminophen is a weak inhibitor of the synthesis of prostaglandins, with evidence suggesting that the analgesic effect results from activation of the descending inhibitory serotonin pathways (e.g., Graham & Scott, 2005; Pickering et al., 2008). While the precise mechanisms by which acetaminophen exerts an analgesic effect remain unclear (Graham et al., 2013), it is widely accepted that this drug reduces pain through central, rather than peripheral, nervous system mechanisms (Anderson, 2008; Courade et al., 2001; Pickering et al., 2006; Smith, 2009). The central activation of acetaminophen means it could also produce varied psychoactive effects, i.e., alterations in other forms of perception, mood, cognition and behavior. In general, psychoactive drugs bypass evolved information processing systems governing behavior and emotions, thus potentially disengaging otherwise adaptive psychological mechanisms and defenses (Nesse & Berrdige, 1997).

In the first study to examine the potential unintended psychological effects of this drug, DeWall et al. (2010) investigated whether acetaminophen altered feelings of psychosocial distress. This work was based on prior neuroimaging research showing that both physical and social pain are processed within the same neurobiological systems, i.e., dorsal anterior cingulate cortex and anterior insula (Apkarian et al., 2005; Eisenberger et al., 2003; Peyron et al., 2000; Rainville et al., 1997). Therefore, the researchers predicted that acetaminophen would reduce social pain by attenuating neural activity within these critical brain regions. It was found that after taking 1,000-2,000 mg of acetaminophen daily for a period of three weeks, participants indeed reported significantly lower levels of social pain in their daily lives and showed reduced neural activation in both the dorsal anterior cingulate cortex and anterior insula to social rejection scenarios produced in a laboratory setting (DeWall et al., 2010).

Subsequent research has now expanded upon these initial findings (Fung & Alden 2017; Slavich et al. 2019), and a growing number of studies have confirmed that even a single 1,000 mg dose of acetaminophen can reduce varied forms of psychosocial distress. In one study, acetaminophen interrupted typical compensatory responses to violations of expectations, also known as meaning threats (Randles et al., 2013). For example, participants given an acute dose of acetaminophen (1,000 mg) experienced less negativity when thinking about their own mortality compared to placebo. Single doses of acetaminophen have also been shown to reduce internal

conflict and pain associated with some forms of decision-making (DeWall et al., 2015) as well as reduce the perceived challenge associated with tasks designed to induce social stress (Bershad et al., 2018).

Acetaminophen has even been shown to reduce empathy for the pain and suffering experienced by others (Mischkowski et al., 2016). In particular, participants administered 1,000 mg of acetaminophen showed reduced personal distress, perceived pain, and empathic concern to hypothetical and laboratory-based scenarios in which individuals experienced both physical and social pain. In a follow-up to this research, the same single dose of acetaminophen also reduced affective reactivity to the positive experiences of others (i.e., positive empathy: Mischkowski et al., 2019). Recent research has also examined the influence of acetaminophen on social economic interactions (Roberts et al., 2018; 2019). For example, participants with elevated personality disorder features showed less trust compared to others when administered a placebo, but showed increased trust (i.e., reduced distrust) when given acetaminophen (Roberts et al., 2018).

Related research indicates that acute doses of acetaminophen can inhibit general forms of evaluative processing through the widespread blunting of cortical activity. In one study, participants were administered either acetaminophen or placebo and asked to rate the positive or negative valence of a series of images, and to respond to how much the images elicited an emotional reaction (Durso et al., 2015). Results revealed that participants in the acetaminophen condition rated both positive and negative images less extremely and less emotionally arousing than those in the control condition. Consistent with these findings, recent electroencephalography (EEG) studies have demonstrated that acetaminophen disrupts evaluative processing in the cortex (Randles et al., 2016) and neurocognitive disengagement during off-task attentional states (Mutti et al., 2019). Despite the growing interest in this area, there are many unresolved and open questions regarding the psychological and neurological effects of this commonly used OTC drug (Ratner et al., 2018).

Extending upon these recent findings, here we investigate whether acetaminophen disrupts the early processing of emotional signals. Past research has shown an evolved tendency for humans to prioritize and automatically orient towards emotional facial expressions (Öhman et al., 2001; Öhman, 2002; Vuilleumier & Schwartz, 2001). For example, happy and angry faces tend to capture and hold our attention (Mack et al., 2002; Torrence et al., 2017). Therefore, the current study tested whether acetaminophen modulates the initial visual processing of emotional facial expressions using a delayed disengagement task (e.g., Belopolski et al., 2011). Given previous research demonstrating that acute doses of acetaminophen diminish affective responses to both positive and negative stimuli (DeWall et al., 2010; Durso et al., 2015; Michkowski et al., 2016; 2019), we hypothesized that the administration of this drug would reduce the typical delay in disengaging from emotional expressions.

METHODS

Participants. A total of 101 (32 female) college students participated in a study investigating the effects of acetaminophen on various aspects of psychological processing from November 2018 to May 2019. Recruitment occurred through the

psychology pool and campus flyers on a public research university in Upstate New York. The data from one participant was removed upon discovering they were 17 years of age. The remaining sample was aged 18-34 years (mean ± SD: 19.61 ± 2.71). Participants received either course research credit or $20 in compensation for their time in the study. Exclusion criteria included any risk factors associated with taking acetaminophen (e.g., currently taking a drug containing acetaminophen, a history of liver disorder, an allergic reaction to acetaminophen or a history of alcohol abuse) or a history of medical or psychiatric illness. The experiment was conducted in accordance with approved human ethics guidelines, and all participants provided informed consent prior to partaking in this study. The local Institutional Review Board approved this research (#2018-08-07-1).

Design. Random assignment determined whether participants consumed a 10 ml liquid containing 1,000 mg of acetaminophen or a matched placebo solution. Similar to Michkowski et al. (2016), acetaminophen and placebo solutions were prepared by Pharmacy Specialists Compounding Pharmacy (Altamonte Springs, Florida). The drug solution consisted of acetaminophen (100 mg/ml) dissolved in Ora-Plus suspension liquid and flavored with Ora-Sweet Syrup and the placebo solution will consist of Avicel Microcrystalline powder (100 mg/ml) dissolved in the same vehicle. Participants and researchers were blind to the experimental condition. Participants were asked to refrain from eating for at least three hours prior to the study, and following administration participants waited for a period of 60 minutes for drug absorption (Randles et al., 2013; Durso et al., 2015).

Following the waiting period, participants were escorted to a cubicle and positioned at a desk approximately 65cm from a Tobii Pro Spectrum 150hz eye-tracker attached to a 60cm stimulus presentation monitor (EIZO FlexScan EV2451). Following a standard 5-point calibration to assess accuracy and precision, participants were instructed on how to perform a delayed disengagement task modified from Belopolski et al. (2011). Specifically, participants were cued to the center of the screen and then presented with a face positioned in between two target boxes (one on the left; one on the right). The faces were 200 x 300 pixels at their greatest dimensions (approximately 4.8 degrees of visual angle wide and 7.1 degrees of visual angle high), and the offset target boxes were 300 x 300 pixels (approximately 6.3 degrees of visual angle wide and 6.3 degrees of visual angle high). Each trial started with a fixation point at the center of the screen for 1350 ms, which was followed by a face at the fixation point for 2000 ms and then a blank screen for 350 ms (Figure 1). Face stimuli included closed mouth depictions of neutral, happy, and angry expressions from the NimStim face set (Tottenham et al., 2009). These images were modified to grayscale and a uniform oval shape (which also removed hairstyles). Each face was tilted 10^{o} on the vertical axis, and participants were instructed to look at the box in the congruent direction of the tilted face as quickly as possible. Hence, if the face was tilted to the left, participants had to fixate on the box on the left (see Figure 1). Both boxes included a target dot which was 742 pixels from the center of the screen. A predefined area of interest (AOI) was drawn over each of the boxes (overlapping the edges by 50 pixels, or approximately 13.4 mm), and responses were measured by the latency (in milliseconds) to fixate on the AOI of the congruent box. Participants were informed that the expression of the face was irrelevant to the task.

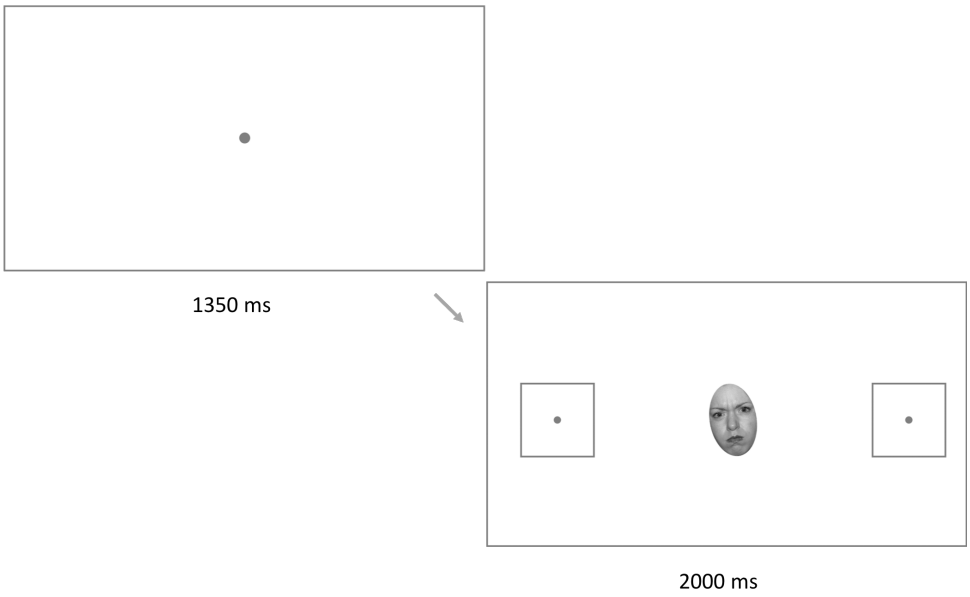

Figure 1. Depiction of the focal point and stimulus presentation for the delayed disengagement task. Represented above is an angry female face tilted to the left; during this trial, participants would avert their attention and fixate on the left box as quickly as possible.

Prior to testing, participants completed 12 practice trials to become familiar with the task. These trials portrayed one male face and one female face in all possible combinations (3 expressions x 2 vertical orientations), and participants received verbal feedback on their performance from a researcher running the session from the other side of a partition. Following the practice trials, participants then completed 96 testing trials separated by a break at the midpoint. These trials portrayed eight male and eight female faces in all possible combinations, with the order randomized prior to testing. Participants were encouraged to respond as quickly and accurately as possible during all trials.

Analysis. During data collection, five participants indicated having an eye condition and/or produced high inaccuracy or imprecision during calibration, and therefore were not included in the analysis. In addition, based on research indicating the time needed before a programed eye movement is launched (e.g., Matin et al., 1993), any trial responses that occurred before 200 ms were excluded from the analysis. Moreover, the data from an entire participant were excluded from the analysis if the individual responded too early (< 200 ms) or too late (> 2000 ms) on more than five of the 96 trials during testing. This included 5% of the total sample (5/100).

The final sample consisted of 90 participants (43 acetaminophen; 47 placebo), all with normal or corrected to normal vision. We ran a mixed-effect ANOVA with facial expression (neutral, angry, or happy) as a within-subject factor and drug treatment (acetaminophen or placebo) as a between-subject factor. A post hoc power analysis was performed for this design using G*Power 3.1, indicating power of 0.846 to detect a small effect. All statistics were conducted in SPSS, with the alpha set to 0.05.

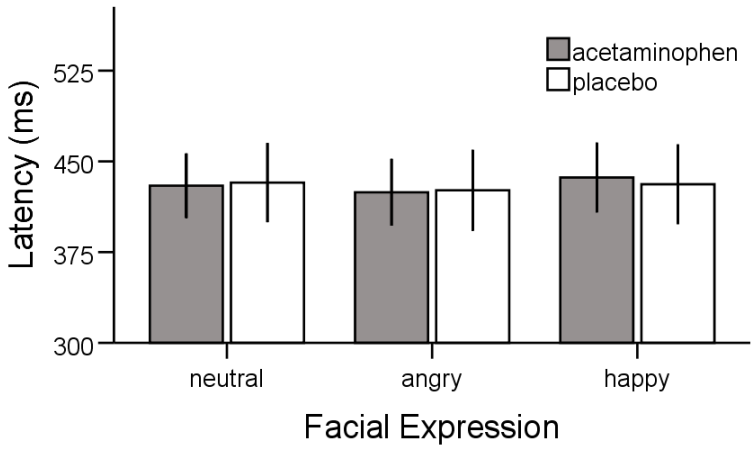

Figure 2. Fixation latencies varied significantly across the three facial expressions ($p < 0.05$), but there was no difference between the acetaminophen and placebo conditions. *M* ± 95% CI represented above.

RESULTS

Analyses revealed a significant main effect of facial expression ($F_{2,176} = 3.927$, $p = 0.021$, *partial eta*$^2 = 0.043$; Figure 2). Post hoc tests revealed that disengagement away from the angry faces was significantly faster compared to both happy faces ($p = 0.008$) and neutral faces ($p = 0.042$). However, there was absolutely no difference between conditions with regards to drug treatment ($F_{1,88} = 0.000$, $p = 0.983$, *partial eta*$^2 = 0.000$). Moreover, there was no interaction between the facial expression and drug treatment conditions ($F_{2,176} = 1.018$, $p = 0.364$, *partial eta*$^2 = 0.011$). Therefore, acetaminophen did not appear to alter visual processing in this task.

DISCUSSION

A growing number of studies have reported distinct psychological effects resulting from the consumption of acetaminophen (reviewed by Ratner et al., 2018). Based on previous work showing that acetaminophen blunts affective responses to positive and negative stimuli (e.g., DeWall et al., 2010; Durso et al., 2015; Michkowski et al., 2016; 2019), this study examined whether this drug influences the early processing of emotional facial expressions. Contrary to our predictions, participants in both the acetaminophen and placebo groups responded similarly across facial expression conditions.

Prior imaging studies have shown that acetaminophen attenuates activity within cortical areas involved in the rapid processing of emotional facial expressions (i.e., the anterior cingulate cortex: DeWall et al., 2010; Fan et al., 2011; Pickering et al., 2015). However, a large number of cortical and subcortical structures become

active during the early processing of emotional faces (e.g., Adolphs, 2002; Fan et al., 2011; Habel et al., 2007; LeDoux, 1995; Morris et al., 1999), and the null effects reported here may be due to greater subcortical activation during the disengagement. In other words, it is possible that the test we used incorporates brain areas that are so evolutionarily conserved, due to the necessity of quickly processing emotions via the face, that the neuromodulation from acetaminophen fails to alter this prewired adaptation. In addition, the nature of focusing on the vertical orientation of the facial stimuli could recruit other brain regions not affected by acetaminophen. Therefore, future research could more explicitly investigate whether this drug modulates the evaluation of more complex emotional states in others. Based on studies showing that acetaminophen inhibits the activation of some emotions (e.g., DeWall et al., 2010; Randles et al., 2013), it would also be interesting to assess whether this OTC drug blunts facial affect display.

Across drug treatment conditions, our results show that happy faces produced the slowest disengagement and angry faces produced the fastest disengagement. These findings are in contrast to those reported in Belopolski et al. (2011), which showed slowest disengagement from angry expressions and no difference between happy and neutral faces. It is not clear why our results differ, particularly given the backdrop of literature showing that biologically threatening stimuli capture attention (e.g., Öhman et al., 2001; Öhman & Mineka, 2001). However, one key distinction in methods is that Belopolski et al. (2011) used schematic faces with more dramatic cues of happiness and anger, while the current study included photographs of people displaying subtle, closed mouth depictions of these emotions (Tottenham et al., 2009). Therefore, it remains possible that the more overt "open mouth stimuli" from the NimStim image set would produce different effects. Nonetheless, prior works have shown that happiness captures attention (Mack et al., 2002; Miyazawa, & Iwasaki, 2010; Torrence et al., 2017), and the main effect observed here is consistent with this literature.

In summary, the results of this study suggest that an acute dose of acetaminophen does not alter the early processing of emotional facial expressions. However, due to limitations in the current approach, we propose that research continue to explore how acetaminophen may alter both the detection and perception of emotion in others. With tens of millions of Americans consuming acetaminophen each week, it is critical for researchers to study the full range of psychological effects produced by this drug if we hope to understand how it influences real-world interactions and interpersonal relationships. Moreover, further research should explore how chronic use of this drug may alter different aspects of neurological/psychological processing. In particular, we believe that further evolutionary inspired research like this could provide important insight into understanding how this common OTC painkiller produces a mismatch with our evolved psychology (Gallup, 2019).

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