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Higher habitual dietary caffeine consumption is related to lower experimental pain sensitivity in a community-based sample

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Abstract

Rationale: Caffeine is the most widely consumed psychoactive substance in the world. Caffeine administered acutely in a laboratory environment or as a medication adjuvant has known properties that help alleviate pain. However, much less is known about the potential impact of habitual dietary caffeine consumption on the experience of pain.

Objectives: The primary objective of this observational study was to determine whether caffeine consumed habitually as part of a daily diet was associated with experimental pain sensitivity using noxious stimuli in a non-clinical sample of 62 community-dwelling adults between 19 to 77 years old.

Methods: Study participants monitored their daily dietary caffeine consumption (e.g., coffee, tea, soda, energy drinks, and chocolate) across a period of seven consecutive days using a caffeine consumption diary. On the seventh day of caffeine consumption monitoring, participants presented to the laboratory to complete experimental pain sensitivity testing. Noxious thermal and mechanical stimuli were used to obtain threshold and tolerance for painful heat and pressure, respectively.

Results: Data analysis revealed that greater self-reported daily caffeine consumption was significantly associated with higher heat pain threshold ($\beta = .296$, $p = .038$), higher heat pain tolerance ($\beta = .242$, $p = .046$), and higher pressure pain threshold ($\beta = .277$, $p = .049$) in multiple regression models adjusted for covariates.

Conclusions: Results of this study completed with community-dwelling adults revealed that individuals who habitually consume greater amounts of caffeine as part of their daily diets demonstrate diminished sensitivity to painful stimuli in a laboratory setting.

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Keywords

caffeine; dietary consumption; pain sensitivity; threshold; tolerance

Introduction

Caffeine is a psychoactive and central nervous system stimulant of the methylxanthine class (Morelli & Simola, 2011). Unlike many other psychoactive substances, caffeine is legal for consumption all around the world, and it is widely consumed. In the United States, estimated average daily caffeine consumption ranges from 165 to 211 mg across children and adults (Fulgoni, Keast, & Lieberman, 2015; Mitchell, Knight, Hockenberry, Teplansky, & Hartman, 2014), which corresponds to roughly two 8 to 10 oz servings of brewed coffee (Mackus, van de Loo, Benson, Scholey, & Verster, 2016; McCusker, Goldberger, & Cone, 2003). Furthermore, approximately 85–95% of American adults consume caffeine on a daily basis (Frary, Johnson, & Wang, 2005; Fulgoni et al., 2015; Mitchell et al., 2014). Evidence suggests that consumption of low to moderate (<400 mg/day) amounts of daily caffeine is safe for healthy adult men and (non-pregnant) women with minimal side-effect burden (Temple et al., 2017; Wikoff et al., 2017). Caffeine is well regarded by consumers for its ability to increase energy, decrease fatigue, promote alertness and wakefulness, and enhance cognitive and physical performance (McLellan, Caldwell, & Lieberman, 2016). However, when consumed in large quantities (>400 mg/day), people may also experience symptoms of acute caffeine intoxication (e.g., insomnia, restlessness, upset stomach, tremor) or caffeine withdrawal when habitual use is attenuated (e.g., headache, irritability, fatigue) (Cappelletti, Piacentino, Sani, & Aromatario, 2015; Meredith, Juliano, Hughes, & Griffiths, 2013). Caffeine occurs naturally in many plants, including coffee beans, tea leaves, and cocoa nuts. It is therefore found in a wide range of food products including coffee, tea, cola, and chocolate (Heckman, Weil, & Gonzalez de Mejia, 2010). Caffeine is artificially added to many other products, including a variety of energy drinks, and over the counter drugs marketed to promote alertness and wakefulness (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007).

In addition to being widely consumed for its central nervous system stimulant effects, caffeine also possesses known pain relieving properties. Laboratory studies conducted in animals and humans have found that the acute administration of caffeine is associated with decreased pain. In preclinical studies, rats demonstrated significantly decreased sensitivity to painful stimuli following acute administration of caffeine, but only at very high doses between 50–100 mg/kg (Sawynok, 2011a). Similarly, a single administration of 250 mg caffeine resulted in significantly higher pain threshold and pain tolerance in response to a cold pressor task (i.e., decreased sensitivity) in a study of healthy humans (Keogh & Witt, 2001). Clinically, caffeine acts as an adjuvant analgesic to decrease pain sensitivity when added in sufficient doses to medications containing aspirin, acetaminophen, and other non-steroidal anti-inflammatory drugs (Derry, Derry, & Moore, 2012). On balance, acute administration of caffeine as a single bolus is appreciated to have therapeutic potential for acute pain management (Baratloo et al., 2016).

Unlike acute intake, habitual (i.e., daily) caffeine consumption at dietary levels is not usually regarded as an analgesic, or appreciated to decrease pain sensitivity, in humans (Derry et al., 2012; Derry, Derry, & Moore, 2014). This is likely because average daily amounts of dietary caffeine consumption are usually much lower (165 – 211 mg) than the large doses of caffeine acutely administered (250 – 400 mg) in the previous studies that have revealed caffeine-induced analgesia. Importantly, the assertion that habitual caffeine consumption at dietary levels is not associated with analgesia or diminished pain sensitivity does not appear to be supported empirically. In fact, it appears that no study to date has actually assessed naturalistic patterns of habitual dietary caffeine consumption over days or weeks in relation to pain. The closest evidence addressing this topic comes from a series of cross-sectional studies that simply asked individuals to self-report their dietary caffeine consumption by history, and the results have been equivocal. Two older studies reported that dietary caffeine consumption was associated with reduced pain sensitivity (Larroque, Kaminski, Lelong, Subtil, & Dehaene, 1993; Leathwood & Pollet, 1982), while a more recent study suggested that dietary caffeine consumption was associated with a modest increase in sensitivity for painful stimuli (Karunathilake, Frye, Stavropoulos, Herman, & Hastie, 2012). It is important to note, however, that none of these previous investigations actually incorporated repeated measurements of daily caffeine consumption across day/weeks; therefore, it is not possible to determine whether these individuals' reports of dietary caffeine consumption were actually representative of their habitual patterns of caffeine intake. Furthermore, heterogeneity in methodology and sample characteristics across this small number of studies hinders that ability to appreciate whether habitual dietary caffeine consumption is indeed associated with sensitivity to painful stimuli. Additional research is needed to better determine whether habitual caffeine consumption at dietary levels is associated with the experience of clinical and experimental pain.

The primary objective of this observational study was to determine whether caffeine consumed habitually as part of a daily diet was associated with experimental pain sensitivity using noxious heat and pressure stimuli in a non-clinical sample of community-dwelling adults. To accomplish this, participants monitored their naturalistic patterns of daily dietary caffeine consumption (e.g., coffee, tea, soda, energy drinks, and chocolate) across a period of seven consecutive days using a caffeine consumption diary. On the seventh day of caffeine consumption monitoring, participants presented to the laboratory to complete pain sensitivity testing. It was hypothesized that increasing amounts of caffeine consumed habitually as part of a daily diet would be associated with higher pain threshold and higher pain tolerance (i.e., decreased pain sensitivity).

Methods

Participants

This study was comprised of 62 healthy, community-dwelling adult volunteers recruited from the University of Alabama at Birmingham (UAB) campus via posted flyers. All participants reported their ethnicity as non-Hispanic and their race as either White or Black. Age ranged from 19 to 77 years old. Interested individuals were assessed for eligibility during an initial telephone screening. Healthy participants were recruited to eliminate

extraneous factors that could potentially influence pain sensitivity, such as pre-existing pain conditions and/or chronic systemic medical disorders. Individuals were excluded from study participation if they self-reported any ongoing chronic pain problems or any episodes of acute pain within the 2 weeks prior to study participation. Additional exclusionary criteria included: (a) age <18 years, (b) current pregnancy, (c) uncontrolled hypertension (i.e., resting blood pressure > 150/95 mmHg) assessed via sphygmomanometer, (d) history of diabetes with neuropathy, (e) history of neurological disorders including stroke or seizure, (f) history of cardiac events including infarction, (g) history of serious psychiatric disorder requiring hospitalization in the past year, (h) current use of opioid medications or other analgesics, and (i) history of cancer.

Procedures

Participants completed two study sessions in a laboratory setting separated by seven consecutive days of daily caffeine consumption monitoring using self-report diaries. During the first study session, participants provided demographic data including age, sex, and ethnicity/race. Current use of tobacco products (e.g., cigarettes, smokeless tobacco) and average number of beverages containing alcohol consumed in a typical week were then assessed. Next, participants completed the Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995) prior to being provided with a wrist-worn actigraph and sleep diaries that were used to monitor seven consecutive nights of sleep in participants' home environment. At the end of the first study session, participants were provided with detailed instructions regarding how and when to complete the daily dietary caffeine consumption diaries, as well as actigraphy and daily sleep diaries. On the seventh day of caffeine consumption and sleep monitoring, participants returned for the second study session to complete pain sensitivity testing with heat and pressure stimuli. These second study sessions were scheduled throughout the day between the hours of 9AM and 5PM. Participants were informed that they could consume caffeine on the day of their second study session, but were asked to refrain from doing so within the three hours prior to pain sensitivity testing. They were also asked to refrain from strenuous exercise and use of tobacco products or alcohol within three hours prior to pain sensitivity testing. This study was approved by the local Institutional Review Board and carried out in accordance with guidelines for the ethical conduct of research. Written informed consent was obtained from each participant prior to study commencement and they were compensated for their involvement.

Measures

Dietary caffeine consumption: Self-reported dietary caffeine consumption data was obtained via daily paper-and-pencil diaries. Participants were instructed to record dietary intake of caffeine in real time each day across the seven-day observation period. Each daily diary was divided into morning (7am-12pm), afternoon (12pm-6pm), evening (6pm-2am), and late night (2am-7am). The diary was further divided into sections for consumption of coffee, tea, soft drinks, energy drinks, chocolate, and caffeine-containing medications whereby the medication name and dosage could be written. Participants were instructed to record the specific name of the caffeine-containing product consumed. Serving sizes (in ounces) and the number of servings were also recorded. The caffeine consumption diary used in this study was adapted from the Caffeine Consumption Questionnaire, a validated

measure for use in adult populations (Shohet & Landrum, 2001). Previous research suggests that self-reported caffeine intake is a reliable representation of actual caffeine intake (Addicott, Yang, Peiffer, & Laurienti, 2009). Caffeine consumption was quantified using standardized values for milligrams (mg) of caffeine per ounce (or dosage) for each consumed substance. These values were obtained from previously published literature on the topic and/or manufacturer's nutritional information, with consideration for preparation style (e.g., brewed coffee, instant coffee, espresso), type (e.g., dark chocolate, milk chocolate), and brand (e.g., Coca-Cola, Mountain Dew) (Barone & Roberts, 1996; Bunker & McWilliams, 1979; Frary et al., 2005). Total dietary caffeine consumption in milligrams was calculated per day, summed across the seven days, and then averaged.

Heat sensitivity: Thermal stimulation was completed according to previously published procedures by our group to assess heat pain threshold (HPTh) and heat pain tolerance (HPTo) using a Medoc Pathway Neurosensory Analyzer (Medoc, Ltd., Ramat Yishai, Israel) with a 30 X 30 mm thermode (Goodin et al., 2017). HPTh and HPTo were assessed using an ascending method of limits, and thermode temperature increased at a rate of .5 ^{0}C/sec from a baseline of 32 ^{0}C until the participant responded by pressing a button on a handheld device. For HPTh, participants indicated when the sensation first became painful, and for HPTo they indicated when the painful sensation was no longer tolerable. Three trials for HPTh and three for HPTo were delivered to the dorsal and ventral aspects of the dominant forearm, respectively. The three individual trials were averaged together to create overall HPTh and HPTo indices, which were subsequently included in data analysis.

Pressure sensitivity: Pressure stimulation was completed according to previously published procedures to assess pressure pain threshold (PPT) on the distal third of the dorsal (non-dominant) forearm and the ipsilateral trapezius (Glover et al., 2012). A computerized algometer (Medoc, Ltd., Algomed, Ramat, Yishai, Israel) was used to deliver noxious pressure (measured in kilopascals, kPa) stimulation via a hand-held stainless steel probe with a circular, rubber-tipped contact surface of 1.0 cm^2. PPT was also assessed using an ascending method of limits, and the pressure increased at a rate of 30 kPa/sec until the participant responded by pushing a button on a handheld device to indicate when the pressure first became painful (i.e., PPT). The algometer was applied three separate times at each anatomic location in an order that was counterbalanced across participants. Results of the three threshold trials completed for each anatomic location were averaged to obtain PPTs for forearm and trapezius that were used in data analysis.

Pain Catastrophizing Scale (PCS): The standard PCS is a 13-item scale that assesses catastrophic thinking in response to pain and includes aspects of magnification, rumination, and helplessness (Sullivan et al., 1995). The standard PCS assesses catastrophic pain-related cognitive-emotional processes by asking participants to recall their experiences during a past occurrence of pain. The PCS total score is calculated by summing the 13-item responses. Higher scores on the PCS are indicative of greater pain-related catastrophizing, with scores >24 suggestive of clinically meaningful catastrophizing (Scott, Wideman, & Sullivan, 2014).

Sleep Monitoring: Objective sleep data was acquired using the Actiwatch2 (Respironics, Bend, OR), a wrist-worn, watch-like actigraph. The Actiwatch2 is a solid-state accelerometer, or movement detector, designed to measure ambulatory activity. It was used to measure daily sleep-wake patterns and record body movement. The Actiwatch2 has good reliability and criterion validity (39, 40). Actigraphy has been shown to be comparable to polysomnography (Blackwell et al., 2008; Kushida et al., 2001), and actigraphic measurement produces valid data in persons with and without chronic pain (O'Donoghue, Fox, Heneghan, & Hurley, 2009; Sadeh, 2011). Study participants were instructed to depress a button (event marker) on the Actiwatch2 at bedtime and upon waking in the morning. These events were also compared to the corresponding sleep diaries participants completed daily. With the aid of these diaries and event markers, researchers used a protocol for actigraphy scoring and set sleep periods. Sleep-wake patterns were extracted from the actigraphy data using the Actiware Sleep version 6.0.8, which bases its algorithm on the amplitude and frequency of detected movements, which were scored in 30-second epochs.

The following parameters were derived from the actigraphy data: total sleep time, sleep onset latency, wake after sleep onset time, and sleep efficiency. Each parameter was averaged across seven nights of actigraphy for overall measures of sleep quality a week prior to the pain sensitivity testing session. Total sleep time was scored as sleep in minutes from sleep onset to sleep offset. Sleep onset latency represents the length of time in minutes it took to transition from fully awake to asleep. Wake after sleep onset was calculated by adding the number of minutes in which participants were awake from sleep onset to final awakening. Sleep efficiency is the ratio of estimated total sleep time divided by total time spent in bed as a percentage times 100, with values closer to 100 meaning the most efficient sleep.

Data Reduction and Analysis

Continuous data are presented as means and standard deviations (SD), while categorical data are presented as frequencies. Differences in participant characteristics were examined using Analysis of Variance (ANOVA) for continuously measured variables and Chi-square for categorically measured variables. Pearson correlations were used to examine zero-order relationships. The associations of habitual dietary caffeine consumption and caffeine consumed the day of pain sensitivity testing with HPTh, HPTo, and PPT were examined using a series of multiple regressions with adjustment for covariates. Effect sizes are presented demonstrating the magnitudes of these associations. By convention, f^2 effect sizes of 0.02, 0.15, and 0.35 are deemed small, medium, and large, respectively. There were no missing data for any of the study variables. All analyses were carried out using SPSS, version 24.

Covariates: Even in non-clinical samples there are likely still confounding factors that relate to experimental pain sensitivity. Participants' sex and racial background, as well as current tobacco use, average weekly alcohol consumption, pain catastrophizing (PCS), and actigraphic sleep efficiency were included as covariates in the analyses presented below. These variables were chosen *a priori* as covariates for the following reasons. Sex and race differences in experimental pain sensitivity have been well documented in the literature

(Bulls et al., 2015; Kim et al., 2017). Caffeine consumption tends to be higher among cigarette smokers, and caffeine is known to enhance the analgesic effects of cigarette smoking (Nastase, Ioan, Braga, Zagrean, & Moldovan, 2007). Mixing alcohol with caffeinated beverages remains a common phenomenon among younger and middle-aged adults (Heinz, de Wit, Lilje, & Kassel, 2013), while moderate alcohol consumption is associated with decreased pain sensitivity (Zale, Maisto, & Ditre, 2015). Furthermore, previous research from our group has shown that pain catastrophizing (Goodin et al., 2009) and poor sleep (Goodin, Smith, Quinn, King, & McGuire, 2012) can both increase sensitivity to painful stimuli. Although all of the objective sleep parameters were examined, it was anticipated that sleep efficiency would be the most relevant for experimental pain sensitivity given that its calculation is derived from the other parameters (e.g., total sleep time = time in bed – sleep onset latency – wake after sleep onset; **sleep efficiency** = (total sleep time/time in bed) * 100) (Ancoli-Israel et al., 2003).

Results

Participant characteristics

Participant characteristics are shown in Table 1. Average daily dietary caffeine consumption across the seven-day observation period was 170.8 mg/day (SD = 178.1), while average caffeine consumption on the day of pain sensitivity testing was 115.1 (SD = 171.2). The mean age of the study sample was 41.9 years (SD = 15.6). The sample was comprised of 56.5% women (the remaining 43.5% were men) and 48.4% non-Hispanic White (the remaining 51.6 were non-Hispanic Black). Approximately 16% of the sample reported current use of tobacco, which included either cigarette smoking, smokeless tobacco, or both. The remaining 84% denied current tobacco use. Average number of beverages containing alcohol consumed on a weekly basis was 1.6 and ranged from 0 to 15. Neither acute pain nor a history of chronic pain was endorsed by any of the participants, and none reported taking any prescribed or over-the-counter pain medications prior to pain sensitivity testing. None of the experimental pain sensitivity measures (i.e., HPTh, HPTo, PPT at the forearm, PPT at the trapezius) significantly differed according to the time of day (morning, early afternoon, late afternoon) when pain sensitivity testing was conducted (all p values > .05).

Descriptive data representing pain catastrophizing and actigraphic sleep parameters are also shown in Table 1. Scores on the PCS, an index of pain catastrophizing, ranged from 0 – 57 with a mean of 8.7 (SD = 9.3), which is suggestive of a low level of pain catastrophizing for the overall study sample (i.e., <24 on PCS). Average nightly total sleep time was 388.3 minutes (SD = 71.8) per night with an average sleep efficiency of 80.4% (SD = 10.2). Average sleep onset latency was 29.3 minutes (SD = 52.8), with an average of 51.6 minutes (SD = 25.7) of wake time after the onset of sleep.

Habitual dietary caffeine consumption and caffeine consumption the day of pain sensitivity testing

Daily dietary caffeine consumption was significantly correlated across the seven-day observation period, which includes the seventh day when experimental pain sensitivity testing was completed (Table 2). This finding suggests stability in caffeine consumption, and

that participants who consumed greater amounts of dietary caffeine tended to habitually do so across the seven-day observation period. As a result, a habitual dietary caffeine consumption variable was calculated as the average caffeine consumption across all seven days of monitoring. Associations among caffeine consumption the day of pain sensitivity testing and the measures of experimental pain sensitivity were examined separately from habitual dietary caffeine consumption to better appreciate any differences between the acute and habitual effects of caffeine consumption on experimental pain sensitivity.

Correlations and differences in participant characteristics

Habitual dietary caffeine consumption was significantly correlated with HPTh, HPTo, and PPT at the trapezius, but not PPT at the forearm (Table 3). Caffeine consumption the day of pain sensitivity testing was significantly correlated with HPTh and HPTo, but not with PPT assessed at either the trapezius or forearm. These findings indicate that the associations of HPTh and HPTo with habitual dietary caffeine consumption and caffeine consumed the day of pain sensitivity testing were quite comparable; however, habitual dietary caffeine consumption was more strongly associated with PPT at both body sites than was caffeine consumed the day of pain sensitivity testing. No other study variable was significantly correlated with habitual daily dietary caffeine consumption or caffeine consumption the day of pain sensitivity testing (Table 3).

HPTo was significantly greater for men compared to women ($F_{1,60} = 7.96$, $p = .006$), as well as for non-Hispanic Blacks compared to non-Hispanic Whites ($F_{1,60} = 7.47$, $p = .008$). There were no other significant differences in HPTh, HPTo or PPT at the forearm or trapezius by sex, ethnicity/race, or current tobacco use. Neither the actigraphic sleep parameters, pain catastrophizing, or average number of alcoholic beverages consumed each week were significantly correlated with HPTh, HPTo, or PPT at either body site (Table 3).

Multiple regression models

Results from a series of adjusted multiple regression models examining the associations of habitual dietary caffeine consumption and experiemental pain sensitivity are presented in Table 4. HPTh, HPTo, and PPT at the trapzieus were included in these analyses given their significant zero-order correlations with habitual dietary caffeine consumption; PPT at the forearm was not included due to a lack of initial significant correlation. Results from these adjusted multiple regression models revealed that increasing amounts of habitually consumed dietary caffeine were significantly associated with higher HPTh ($\beta = .296$, $p = .038$, $f^2 = .081$), higher HPTo ($\beta = .242$, $p = .046$, $f^2 = .054$), and higher PPT at the trapezius ($\beta = .277$, $p = .049$, $f^2 = .071$). Specifically, each additional 100 mg of daily caffeine consumed was associated with a $.5^0$C increase in HPTh, a $.2^0$C increase in HPTo, and a 31.2 kPa increase in PPT at the trapezius. Taken together, these findings suggest that greater reported habitual dietary caffeine consumption was associated with decreased experimental pain sensitivity for noxious heat and pressure stimuli. Two additional multiple regression models were analyzed for HPTo and HPTh that included all of the same covariates as well as caffeine consumed the day of pain sensitivity testing. Controlling for covariates, results revealed that caffeine consumed the day of pain sensitivity testing was also signficantly associated with greater HPTh ($\beta = .316$, $p = .037$, $f^2 = .082$) and HPTo ($\beta = .312$, $p = .015$,

f^2 = .079), such that each additional 100 mg of caffeine consumed the day of pain sensitivity testing was associated with a .5^{0}C increase in HPTh and a .3^{0}C increase in HPTo. PPT at the forearm and trapezius was not included in any multiple regression model with caffiene consumed the day of pain sensitivity testing due to lack of initial significant correlations.

Discussion

This observational study sought to better understand the relationship between habitual dietary caffeine consumption and experimental pain sensitivity using noxious heat and mechanical stimuli. Results support our hypothesis that increasing amounts of caffeine consumed habitually as part of a daily diet would be associated with decreased pain sensitivity, represented in this study as higher pain thresholds and higher pain tolerance. It has previously been asserted, albeit with minimal empirical support, that habitual caffeine consumption at dietary levels does not produce analgesia or decrease pain sensitivity in an appreciable manner (Derry et al., 2012, 2014). However, this study's findings contradict this assertion and suggest that increasing amounts of caffeine consumed as part of the daily diet may be sufficient to alter the nociceptive processing of pain signals in ways that significantly decrease sensitivity to painful stimuli. Given that caffeine consumption the day of pain sensitivity was also significantly related to increased threshold and tolerance for a painful heat stimulus, we cannot rule out the possibility that the acute effects of caffeine were driving the diminished experimental pain sensitivity seen among those who habitually consumed greater amounts of caffeine on a daily basis. Interestingly, neither pain catastrophizing or sleep were found to be significantly associated with experimental pain sensitivity in this study, which is inconsistent with previous findings by our study team (Goodin et al., 2009; Goodin et al., 2012). One possible explanation may be that the current study included a healthy, non-clinical sample of adults who reported minimal pain catastrophizing along with relatively good sleep quality. Pain catastrophizing and poor sleep appear to be more robustly related to pain sensitivity in clinical samples that include patients with chronic pain (Finan, Goodin, & Smith, 2013; Quartana, Campbell, & Edwards, 2009).

Mechanistically, the pharmacological actions of caffeine are attributed primarily to the antagonism of the four adenosine receptors, A_1, A_{2a}, A_{2b}, and A_3 (Ribeiro & Sebastiao, 2010). As it relates to analgesia and decreased experimental pain sensitivity, effects appear to depend on the particular receptor subtype antagonized, as well as the site of action (periphery, spinal cord, supraspinal sites) (Sawynok, 2011b). Adenosine is an inhibitor of neuronal activity in the peripheral and central nervous systems. Consistent evidence shows that antagonism of adenosine receptors by caffeine leads to decreased pain signaling in animal models of neuropathic, nociceptive, and inflammatory pain (Sawynok, 2016). Similarly, studies conducted in humans with spinal cord injury have shown that the antagonism of adenosine receptors (particularly A_1) by caffeine attenuates hypersensitivity to pain, usually caused by damage to nociceptors (Rivera-Oliver & Diaz-Rios, 2014). Taken together, it stands to reason that the effects of habitual dietary caffeine consumption on experimental pain sensitivity observed in this study may also be mediated by the antagonism of adenosine receptors; however, additional research is needed to confirm this possibility. For example, repeated antagonism of adenosine receptors may produce noticeably diminished pain sensitivity over time among those individuals who habitually consume the

highest daily amounts of caffeine. In turn, these individuals develop a greater sense of pain self-efficacy and adept ability to cope with a painful stimulus, which could be explained, in part, by the low levels of pain catastrophizing observed in this sample.

In two systematic reviews, it has been concluded that up to 400 mg/day of caffeine is not associated with adverse health effects (Temple et al., 2017; Wikoff et al., 2017). However, habitual caffeine intake at levels >400 mg/day may be associated with negative health consequences, and certain groups such as those with hypertension, the elderly, children, and pregnant women may be increasingly vulnerable to caffeine side-effects at lower doses (Higdon & Frei, 2006). In this study, those with the highest levels of habitual dietary caffeine consumption reported the least amount of sensitivity to the painful stimuli. It should be noted though that the maximum average daily consumption of dietary caffeine was 643.6 mg, and 14.5% of the study sample reported average daily caffeine consumption levels >400 mg. Habitual dietary caffeine consumption at levels this high may confer pain diminishing effects, but could also possibly be detrimental to health. For this reason, our findings must be regarded with caution. Although rare, caffeine overdose is a possibility (Campana, Griffin, & Simon, 2014). Therefore, the use of caffeine as an analgesic, or for any other health-promoting benefit, must be done responsibly and with consideration for the upper limit of safe daily dosing.

There are several study limitations that warrant mentioning. First, although self-report measures of daily caffeine consumption are a valid method of predicting actual caffeine levels (Addicott et al., 2009), this study did not include any other objective methods for corroborating participants' self-report. As a result, we could not confirm the accuracy of self-reported daily caffeine intake. Second, the cross-sectional and observational nature of the data collected preclude us from making any causal statements regarding the effects of habitual dietary caffeine consumption on experimental pain sensitivity. Alternatively, in this study it could have been that individuals with diminished pain sensitivity consume more dietary caffeine on a daily basis; therefore; pre-existing differences in pain sensitivity between high and low dietary caffeine consumers could account for our study results. Third, the current study's observational design precludes us from being able to disentangle the association of diminished experimental pain sensitivity with habitual dietary caffeine consumption from that of caffeine consumed the day of pain sensitivity testing (i.e., the acute effect). Additional research incorporating an experimental design with longitudinal measurements will be necessary to disentangle the cause and effect relationship between habitual dietary caffeine consumption, the acute effects of caffeine, and the experience of pain. Fourth, this study included a non-clinical sample of healthy adults as participants. The clinical relevance of our findings is unclear given that no conclusions can be drawn about the potential impact of habitual dietary caffeine consumption on the experience of chronically painful conditions. Lastly, we asked participants to refrain from consumption of caffeine, alcohol, and tobacco products, as well as engagement in strenuous exercise within three hours prior to pain sensitivity testing. We relied upon participants' self-report that they did indeed abstain per our request; however, no other objective methods were incorporated to verify participants' self-report.

Despite these limitations, this study provides novel evidence suggesting that greater levels of habitual dietary caffeine consumption may alter the nociceptive processing of pain signals, resulting in decreased sensitivity to painful thermal and mechanical stimuli. This study meaningfully contributes to the current literate by suggesting that, much like the acute administration of a single bolus of caffeine, habitual dietary caffeine consumption may possess analgesic properties that result in decreased pain sensitivity. However, additional translational research incorporating experimental study designs is needed to causally demonstrate that habitual dietary caffeine consumption alters the processing of pain signals, perhaps via repeated antagonism and adenosine receptors. Future research would also benefit from further investigating the effects of habitual dietary caffeine consumption and acute caffeine administration (both as a standalone and adjuvant) in clinical populations with chronic pain. Furthermore, future studies should collect more detailed information regarding tobacco, alcohol, and illicit substance use so that potential covariates of caffeine consumption and alterations in experimental pain sensitivity may be more adequately controlled in multiple regression models. Lastly, it remains to be determined whether the development of caffeine tolerance due to habitual consumption impacts pain sensitivity through the upregulation of adenosine receptors. Such work could shed new light on the potentail health-promoting benefits of a diet that includes appropriate amounts of regular caffeine consumption, particularly in relation to pain management (Grosso, Godos, Galvano, & Giovannucci, 2017; Nehlig, 2016).

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Table 1:

Participant characteristics (N = 62)

Variable	Mean (SD) or %	Range
Sex		
Men	43.5%	
Women	56.5%	
Ethnicity/Race		
Non-Hispanic Black	51.6%	
Non-Hispanic White	48.4%	
Current Tobacco Use		
Yes	16.1%	
No	83.9%	
Average Number Weekly Alcoholic Beverages Consumed	1.6 (2.8)	0 - 15
Age - years	41.9 (15.6)	19 - 77
PCS	8.7 (9.3)	0 - 57
Sleep Onset Latency	29.3 (52.8)	2 – 292.8
Wake After Sleep Onset	51.6 (25.7)	14.3 – 118.6
Total Sleep Time	388.3 (71.8)	209 - 614
Sleep Efficiency (%)	80.4 (10.2)	38.5 – 96.5
Average Daily Dietary Caffeine Consumption (mg) – 7 days	170.8 (178.1)	0 – 643.6
Average Caffeine Consumption Day of Pain Testing (mg)	115.1 (171.2)	0 – 608.8
HPTh	44.9 (3.1)	36 – 49.4
HPTo	48.5 (1.8)	42.3 – 51.5
PPT - Forearm	415.3 (177.6)	148.9 – 1000.1
PPT - Trapezius	464.6 (213.2)	147.6 – 1000.1

Note: SD = standard deviation; BMI = body mass index; PCS = Pain Catastrophizing Scale; PSQI = Pittsburgh Sleep Quality Index; mg = milligrams

Table 2:

Pearson's correlations across the seven-day observation period for dietary caffeine consumption

Variable	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Day 1	—					
Day 2	.817***	—				
Day 3	.786***	.799***	—			
Day 4	.731***	.775***	.819***	—		
Day 5	.655***	.757***	.683***	.762***	—	
Day 6	.613***	.618***	.813***	.691***	.716***	—
Day 7	.745***	.744***	.719***	.698***	.829***	.726***

* = p < .05

** = p < .01

*** = p < .001

Table 3:

Pearson's correlations among continuously-measured variables.

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Habitual Dietary Caffeine Consumption	___										
2. Caffeine Consumption Day of Pain Testing	.829**	___									
3. PCS	-.230	-.198	___								
4. Average # of Weekly Alcoholic Beverages	.193	.184	-.146	___							
5. TST	.168	.137	-.122	-.030	___						
6. WASO	-.129	-.130	.347**	-.004	-.053	___					
7. SOL	-.102	-.069	.018	-.097	-.386**	-.034	___				
8. SE	.178	.132	-.354**	.003	.634**	-.515**	-.528**	___			
9. HPTh	.305*	.285*	-.023	.033	-.019	-.189	.070	.133	___		
10. HPTo	269*	.286*	-.027	.125	-.116	-.158	-.005	-.018	.670**	___	
11. PPT - Forearm	.149	.096	-.161	-.064	-.082	-.209	.183	.120	.414**	.276*	___
12. PPT - Trapezius	.288*	.175	-.132	.146	-.056	-.002	-.006	-.008	.409**	.348**	.719**

* = $p < .05$

** = $p < .01$

Note: PCS = Pain Catastrophizing Scale; TST = total sleep time; WASO = wake after sleep onset; SOL = sleep onset latency; SE = sleep efficiency; HPTh = heat pain threshold; HPTo = heat pain tolerance; PPT = pressure pain threshold.

Table 4:

Multiple regression models predicting HPTh, HPTo, and PPT at the trapezius.

Variables	R^2	B	SE B	β	Sig
HPTh	.123				.399
Sex[a]		-1.077	.830	-.185	.200
Race[b]		.140	.788	.024	.860
Tobacco Use[c]		-.258	1.145	-.033	.823
Avg # of Weekly Alcoholic Beverages		-.015	.143	-.014	.920
PCS		.010	.045	.032	.824
Sleep Efficiency		.041	.042	.144	.330
Habitual Dietary Caffeine Consumption		.005	.002	.296	**.038**
HPTo	.356				**.001**
Sex[a]		-1.408	.409	-.421	**.001**
Race[b]		1.113	.388	.335	**.006**
Tobacco Use[c]		.232	.564	.052	.683
Avg # of Weekly Alcoholic Beverages		-.004	.071	-.007	.955
PCS		-.012	.022	-.068	.578
Sleep Efficiency		-.005	.020	-.032	.800
Habitual Dietary Caffeine Consumption		.002	.001	.242	**.046**
PPT - Trapezius	.139				.306
Sex[a]		-86.789	56.692	-.216	.132
Race[b]		-34.103	53.841	-.086	.529
Tobacco Use[c]		-33.413	78.234	-.062	.671
Avg # of Weekly Alcoholic Beverages		7.858	9.776	.110	.425
PCS		-2.748	3.050	-.128	.372
Sleep Efficiency		-.706	2.839	-.036	.805
Habitual Dietary Caffeine Consumption		.312	.155	.277	**.049**

Note: HPTh = heat pain threshold; HPTo = heat pain tolerance; PPT = pressure pain threshold; PCS = Pain Catastrophizing Scale; Avg = average

[a]Sex coded 1 = Men, 2 = Women

[b]Race coded 1 = Black, 2 = White

[c]Tobacco use coded 1 = Not currently using, 2 = Currently using