Pain Modulation in Tension-Type and Migraine Headaches: The Offset Analgesia Effect

A dissertation presented to
the faculty of
the College of Arts and Sciences of Ohio University

In partial fulfillment
of the requirements for the degree
Doctor of Philosophy

Kristin N. Lewis
December 2014

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This dissertation titled

Pain Modulation in Tension-Type and Migraine Headaches: The Offset Analgesia Effect

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ABSTRACT

LEWIS, KRISTIN N., M.S., December 2014, Psychology

Pain Modulation in Tension-Type and Migraine Headache: The Offset Analgesia Effect

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Objective: Migraine and Tension-type headaches are common and disabling disorders, but their pathophysiologies are poorly understood. Dysfunctional pain inhibition is postulated to contribute to the development and/or maintenance of these disorders. Offset analgesia, a temporal contrast effect which activates brain structures involved in pain modulation, has never been assessed in headache sufferers. The object of the study was to compare the offset analgesia effect in a group of headache sufferers to a group of healthy controls.

Methods: Undergraduate college students (N=111) were recruited through a research participant pool, and were compensated for their participation with research credit. Participants provided demographic and inclusion/exclusion information, and completed a diagnostic interview for headache disorders. Next, participants established their pain threshold for a temperature stimulus. This temperature was used in the offset analgesia procedure in which participants were asked to continuously rate a series of 3 temperatures: 5 seconds at pain threshold, 5 seconds at 1 degree Celsius above pain threshold, and 15 seconds at pain threshold.

Results: Participants with headaches reported an average of 41 headaches a year, with the most common diagnosis being Frequent Episodic Tension-type (30%), followed by Migraine (26%), Infrequent Episodic Tension-type (9%), and Mixed (7%). Although
offset analgesia was observed, $t (99) = 3.54, p < .01$, there was no significant difference in the degree of offset analgesia when healthy controls were compared to those with migraine or tension-type headache, $F (2, 88) = 1.17, p = .31$. Degree of offset analgesia also did not differ as a function of headache frequency, $r < 0.04, n=76, p=.96$.

Conclusions: The current study demonstrated offset analgesia in a sample of young adults, and provides the first evidence that this form of pain modulation is not associated with headache symptoms. It should be noted, however, that differences may yet be observed in a clinical population with more severe and/or prolonged headache history.
ACKNOWLEDGMENTS

I would like to thank Dr. Christopher R. France for his seemingly endless patience, support, and generosity with his time. His guidance has helped shape my development as a researcher and my understanding of Health Psychology. I would also like to thank Dr. Stephen Patterson, Dr. Peggy Zoccola, Dr. Christine Gidycz, Dr. Betty Sindelar, and Dr. Biing-Jiun Shen for advising me through the course of this project. In addition, Bob Conaster provided essential technical and programming support. Finally, I am grateful for the invaluable feedback, encouragement, support, and humor provided by my lab mates, family, and friends throughout my graduate career.
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INTRODUCTION

Headache disorders are both diverse and pervasive, with a global lifetime prevalence for all headache disorders of approximately 66% (Stovner et al., 2007). The two most common forms of headache are tension-type headache and migraine headache (Jensen & Stovner, 2008; Stovner et al., 2007). These disorders pose serious public health problems, including high rates of physical impairment, employment absenteeism, reduced work productivity, and diminished quality of life (Holroyd, 2002; Holroyd et al., 2000; Hu, Markson, Lipton, Stewart, & Berger, 1999; Schwartz, Stewart, Simon, & Lipton, 1998).

Given the prevalence and impact of tension-type headaches, the most common group of headache disorders, it is surprising that their pathophysiology remains poorly understood. However, based on growing evidence that individuals with tension-type headaches show an exaggerated response to noxious stimuli when compared to healthy controls (e.g. Ashina, Bendtsen, Ashina, Magerl, & Jensen, 2006; Fernandez-de-Las-Penas, Cuadrado, Arendt-Nielsen, Ge, & Pareja, 2007), it has been proposed that a dysregulation of central pain modulation may be a key contributor to tension-type headache disorder (Ashina et al., 2006; Bendtsen et al., 2010). One potential form of dysregulation of pain modulation may be decreased inhibition of nociceptive input from supraspinal (i.e. brain) structures (Bendtsen et al., 2010).

Despite the theorized input of the nociceptive systems to the pathophysiology of tension-type headache disorders, few studies have been conducted examining the functioning of these systems in individuals with the disorder (Ashina, Bendtsen, &
Ashina, 2005; Cathcart, Winefield, Lushington, & Rolan, 2010). However, initial work in the area appears promising; several authors have found abnormal inhibitory responses in patients with chronic tension-type headaches using both conditioned pain modulation and the exteroceptive second silent period methodologies (Pielsticker, Haag, Zaudig, & Lautenbacher, 2005; Sandrini et al., 2006). Additionally, one study found evidence suggestive of dysfunctional antinociception based on brain mapping technology. Buchgreitz, Egsgaard, Jensen, Arendt-Nielson, and Bendtsen (2008) used high-density electroencephalographic (EEG) mapping, a technique for topographic display and analysis of brain electrophysiological data, to investigate the processing of muscle pain in chronic tension-type headache sufferers. Patients demonstrated an abnormal pattern of EEG activity in response to prolonged pain as compared to healthy controls. Specifically, healthy controls demonstrated a reduction in the magnitude of brain activation towards the end of a series of painful stimuli, while chronic tension-type headache patients did not demonstrate this reduction. This absence of a reduction in brain activation in chronic tension-type headache patients may suggest deficient descending inhibition.

The pathophysiology of migraine disorders, the most disabling form of headache, is also surprisingly unclear (Holland & Afridi, 2014; Charles, 2012; Goadsby, 2012). Current theories consider it a disorder of the brain in which the trigeminovascular system’s function influences the pain of the attack. Specifically, the activation of the meningeal and blood vessel nociceptors combined with disrupted central pain modulation leads to the perception of pain (Holland & Afridi, 2014; Silbertstein, 2006). There is a preponderance of support for the dysregulation of pain processing in individuals with
migraine headache. Cutaneous allodynia—the perception of nonnoxious stimuli as noxious—is perhaps the most consistent finding of impaired pain perception in participants with migraine headache in both clinical and experimental settings (i.e., Burstein, 2000, Goadsby, 2012; Gobel, Weigle, Kropp, & Soyka, 1992; Lous & Olesen, 1982). Impaired habituation to repeated noxious stimulation (e.g., Coppola, Pierelli, & Schoenen, 2009; De Marinis, Pujia, Natale, D’arcangelo, & Accomero, 2003; Goadsby, 2006; Schoenen, 1996; Valeriani et al., 2003) and a failure of conditioned pain modulation (e.g. de Tommaso et al., 2007a, 2007b; Coppolla et al., 2010; Sandrini et al., 2006) have also been consistently demonstrated in participants with migraine. Finally, when compared to healthy controls, participants with migraine have been shown to have reduced grey matter volume in the bilateral insula, motor/premotor, prefrontal, cingulated cortex, right posterior parietal cortex, and orbitofronal cortex. Additionally, a negative correlation was found between reduction in grey matter and both headache duration and frequency, such that reduced grey matter was associated with increased headache duration and lifetime headache frequency (Kim et al., 2008). Taken together, these findings suggest that dysfunctional pain processing, and impaired descending inhibition specifically, may contribute to migraine pathophysiology.

As shown above, the pathophysiology of both migraine and tension-type headache are areas in need of continued research. Additionally, there is evidence to suggest that a component of the etiology of both forms of headache involves dysfunctional antinociception. Therefore, the current study examined descending pain modulation in individuals with and without migraine and tension-type headache using a
recently developed paradigm known as “offset analgesia.” Offset analgesia, originally demonstrated by Grill and Coghill (2002), refers to a dramatic decrease in perceived pain intensity disproportionate to a small decrease in noxious thermal intensity. The offset analgesia protocol has been fairly consistent across studies: the participant rates pain intensity while experiencing a 45°C heat stimulation for 5 seconds (T1), followed by a slightly increased temperature to 46°C for 5 seconds (T2), and finally, the temperature is returned to the original, T1 temperature of 45°C (T3). The experimental protocol also frequently includes a trial in which the temperature returns to a non-noxious baseline during T3 (control trial) in order to demonstrate the robustness of the offset analgesia effect in comparison. Additionally, in order to control for habituation (decreased perception of pain over time), studies frequently include trials in which the temperature remains constant from T1 to T3 (see Figure 1, e.g., Derbyshire & Osborne, 2008; Grill & Coghill, 2002).

There is mounting evidence that offset analgesia is a form of central pain modulation. Derbyshire and Osborn (2009) and Yelle, Oshiro, Kraft, and Coghill (2009), found that the regions of the brain closely connected with pain modulation, such as the RVM and PAG, demonstrate activation patterns which correspond with the offset analgesia effect. These regions have not been shown to be activated in conditioned pain modulation procedures (Villanueva & Le Bars, 1995). As further demonstration of the independent contribution of conditioned pain modulation and offset analgesia to pain modulation, offset analgesia is not affected by the infusion of substances such as ketamine, morphine, naloxone, and remifentanil, substances which impact conditioned
pain modulation (Martucci, Eisenach, Tong, & Coghill, 2012; Niesters et al., 2011a; Niesters, Hoitsma, Sarton, Aarts, & Dahan, 2011). Additionally, the offset analgesia effect was found to be reduced in a small sample of patients with chronic neuropathic pain; implying that for patients with pain disorders specifically, offset analgesia may offer an indicator or measure of dysfunctional pain modulation (Niesters, et al, 2011b). To date, offset analgesia has only been assessed in the context of neuropathic pain; hence, the paradigm offers an exciting new method to examine endogenous central pain modulation in participants with headache concerns.

The current study compared the magnitude of the offset analgesia effect in individuals with both migraine and tension-type headaches to healthy controls. Based on previous findings suggesting that individuals with both migraine and tension headaches have dysfunctional central modulation of pain, and that offset analgesia involves central pain modulation, we predicted that participants with migraine and tension-type headaches would have a smaller magnitude of offset analgesia than healthy controls.
METHOD

Participants

All participants were recruited from the Ohio University Psychology Department’s online pool of college students enrolled in undergraduate psychology courses. Participants received two credits towards fulfilling a research requirement. Due to high rates of psychiatric comorbidity in headache sufferers, measures of anxious and depressive symptoms were administered to all participants in order to characterize the sample and enable comparison with previous studies (Holroyd et al., 2010). Additionally, in order to further characterize the sample and identify potential confounds, brief measures of sleep, alcohol use, caffeine intake, stress, physical activity, pain anxiety, and pain catastrophizing were completed by participants. For an overview of the flow of participants through the study, please see Figure 2.

Measures

**Headache Measures**

Both the Headache Screening Questionnaire (BSQ) and the Structured Diagnostic Interview for Headache (SDIH) are based on the diagnostic criteria for migraine and tension-type headaches developed by the Headache Classification Committee of the International Headache Society (2004).

*Headache Screening Questionnaire.* A modified version of the Headache Screening Questionnaire (Holm, 1983) was used to ascertain the frequency and type of headaches experienced. This instrument includes a total of 22 questions about chronicity, duration, intensity, frequency, familial history and quality of headaches, as well as
previous medication use and presence of concurrent pain disorders. This self-report questionnaire has been consistently used as an effective screener for headache experience among college student populations (Gunstad & Suhr, 2001; Holm, 1983; Holroyd & French, 1995; Houle, Penzien, & Rains, 2005; Houle, Dhingra, Remble, Rokicki, & Penzien, 2006; Janke, Holroyd, & Romanek, 2004).

Structured Diagnostic Interview for Headache, Brief Version (SDIH). All individuals who agreed to participate in the study were interviewed by the primary investigator using the Structured Diagnostic Interview for Headache, Brief Version (Houle, et al., 2005; Lipchik et al., 1996; Lipchik, Holroyd, Talbot, & Greer, 1997; Neufeld, Holroyd, Lipchik, 2000). The purpose of this interview was to confirm the headache subtype indicated by the screening questionnaire and to clarify any areas of ambiguity. The interview includes 20 questions regarding: pain quality, headache location, onset, chronicity, frequency, duration, intensity, previous treatments, headache history and associated symptoms, family history, and general medical/medication history. The SDIH has been used repeatedly in prior research for diagnostic purposes (Houle et al., 2005; Janke, Holroyd, & Romanek, 2004; Lipchik et al., 1996, 1997; Neufeld et al., 2000), has demonstrated consistency in the ability to distinguish between headache diagnoses (Lipchik et al., 1996; 1997), and research participants identified using the SDIH share symptoms with patient samples that have been clinically diagnosed (Lipchik et al., 1996; 1997).
Secondary Measures

The following measures were not the primary focus of the study but were included due to their relevance to both headache disorders and pain. For example, catastrophizing has been found to increase the impact of headache and pain in general (Holroyd, Drew, Cottrell, Romanek, & Heh, 2007; Ruscheweyh, Nees, Marziniak, Evers, Flor, & Knecht, 2011), and depression and anxiety have been correlated with both headache frequency and chronic pain (i.e. Banks & Kerns, 1997; Bhegi et al., 2007; Mitsikostas & Thomas, 1999). Obesity has been related to the chronification of headache disorders (Scher et al., 2003). Additionally, fatigue, stress, physical activity, caffeine use, and alcohol use are common headache triggers (Spierings, Ranke, & Honkoop, 2001).

Situational Catastrophizing Questionnaire (SCQ; Edwards, Smith, Stonerock, & Haythornthwaite, 2006). The SCQ is a modified form of the Pain Catastrophizing Scale that assesses situational pain catastrophizing. Participants completed the six SCQ items (e.g., “I thought that the pain might overwhelm me”) rated on a 0 (“not at all”) to 4 (“all the time”) scale, indicating the degree to which they had the thought or feeling described during the preceding pain testing session (α = .82). Situational catastrophizing scores are more strongly associated with experimental pain than the global Pain Catastrophizing Scale (Campbell et al., 2010).

McGill Pain Questionnaire-Short Form (SF-MPQ; Melzack, 1987). The SF-MPQ includes 15 pain descriptors that participants rated on a scale from 0 (“mild”) to 3 (“severe”). Pain descriptors include both sensory (“sharp”) and affective (“punishing”) words, and can be presented as a total sum (current study α = .85). This commonly-used
measure of pain is sensitive to treatment for pain and has been correlated with depression, anxiety, and somatization (Melzack, 1987).

*Brief Pain Inventory* (BPI; short form; Daut, Cleeland, & Flanery, 1983). The BPI is an 11 item self-report questionnaire designed to assess both pain intensity and pain interference (current study total $\alpha = .93$). Pain intensity questions ask participants to rate their pain over a series of time-frames on a scale from 0 (no pain) to 10 (pain as bad as you could imagine, $\alpha = .74$). Pain interference items ask participants to rate the degree to which their pain interferes with a series of general and specific activities of daily living (i.e. general activity, normal walking) on a scale of 0 (does not interfere) to 10 (interferes completely, $\alpha = .94$). Participants were asked to rate their headache-related pain using this scale. The BPI has been used to measure pain related to a variety of conditions and has been shown to clarify levels of pain severity and changes in pain severity over time (Keller et al., 2004).

*Headache Disability Inventory* (HDI; Jacobson, Ramadan, Aggarwal, & Newman, 1994). The HDI assesses the burden of headaches with 25 items that inquire into the perceived impact of headaches on emotional functioning (subscale 1) and daily activities (subscale 2). The HDI is able to distinguish between severe, moderate, and mild headaches, but does not distinguish between headache types (Jacobson et al., 1994). Consistent with previous research, the HDI was scored as one total scale (current study $\alpha = .93$). The HDI correlates positively and significantly with headache frequency and severity, providing support for its validity (Jacobson, Ramadan, Aggarwal, & Newman, 1994).
State Trait Anxiety Inventory Form Y (STAI; Spielberger, 1983). The STAI is a self-report questionnaire designed to measure both current (state) anxiety and longstanding (trait) anxiety. The current study included only the 20 questions pertaining to trait anxiety, with 4 options ranging from “almost never” to “almost always” ($\alpha = .93$). Concurrent validity for the STAI-trait is high, in that it is correlated with the Manifest Anxiety Scale and the Anxiety Scale Questionnaire (Spielberger & Reheiser, 2009).

Center for Epidemiologic Studies Depression Scale-Revised (CES-D-R; Eaton, Muntaner, Smith, Tien, & Ybarra, 2004; Radloff, L.S., 1977). The CESD-R is a 20 item self-report questionnaire that is used to assess the presence and severity of depressive symptoms. Items on the CESD-R correspond to the symptoms of depression as defined by the American Psychiatric Association Diagnostic and Statistical Manual (4th ed., text rev.; 2000; Eaton et al., 2004), and clinical populations report higher scores than non-clinical populations (Van Dam & Earleywine, 2011). Items are scored on a 4 point Likert scale based on participants’ choice from a list of four possible responses arranged in increasing severity ($\alpha = .86$).

Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995). The PCS was used to assess participants’ trait pain catastrophizing using thirteen items (e.g., “I worry all the time about whether the pain will end”) rated on a 0 (“not at all”) to 4 (“all the time”) scale. Items are rated as to how well each statement generally describes the participant when he or she is in pain ($\alpha = .90$). Scores on the PCS have been correlated with strength deficits, pain, and disability following an injury (Leung, 2012).
The Pain Anxiety Symptoms Scale- Short Form (PASS-20; McCracken & Dhingra, 2002) measures cognitive anxiety symptoms, escape and avoidance responses, fearful appraisals of pain, and physiological anxiety symptoms related to pain. Items (e.g., “When I feel pain, I am afraid that something terrible will happen”) are rated on a 0 (“never”) to 5 (“always”) scale, reflecting how often the participant feels this way when in pain (α = .92). The PASS-20 has been correlated with measures of pain, depression, and disability (McCracken & Dhingra, 2002).

The Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used to measure how much sleep participants have gotten over the last month and what the quality of that sleep has been, (α = .65). The PSQI includes 19 self-reported questions. The global score of the PSQI has been show to be highly correlated with a sleep diary, and reliably distinguished between individuals who were defined as high fatigue and low fatigue by the Schwartz Cancer Fatigue Scale (Carpenter & Andrykowski, 1998; Grander, Kripke, Yoon, & Youngstedt, 2006).

The Weekly Caffeine Intake Survey (France & Ditto, 1989) was used to assess average weekly caffeine intake by inquiring about the frequency of the participant’s consumption of the most commonly consumed caffeinated beverages (e.g., coffee, tea, soft drinks). Similar measures are highly correlated with 24-hour dietary recalls (Schliep et al., 2013).

The 7-day Physical Activity Recall Questionnaire (Blair, 1984) assesses the frequency of light (e.g. slow walking), moderate (e.g., raking, brisk walking), hard (e.g., scrubbing floors, tennis), and very hard (e.g., carrying heavy loads, jogging) exercise
engaged in over the last week ($\alpha = .73$). The 7-day Physical Activity Recall Questionnaire has been correlated with a daily diary of physical activity and a measure of cardiopulmonary fitness (Dishman & Steinhardt, 1988).

*The Alcohol Use Detection Identification Test* (AUDIT; Saunders et al., 1993) is a 10 item self-report measure designed to assess alcohol consumption, drinking behavior, and alcohol-related problems (e.g., “How often during the last year have you had a feeling of guilt or remorse after drinking?”; $\alpha = .79$). Indicators of alcohol-related concerns and dependence are positively correlated with AUDIT scores (Donovan et al., 2006).

*The Perceived Stress Scale* (PSS; Cohen, Kamarck, & Mermelstein, 1983) is a 10 item measure assessing stress perception during the last month. Items (e.g., “In the last month, how often have you felt nervous and ‘stressed’?”) are rated from 0 (“never”) to 4 (“very often”; $\alpha = .83$). Scores on the PSS have been correlated with the number of number of negative life events an individual has experienced and are higher in parents of children with chronic illness (Lee, 2012)

**Apparatus**

Thermal stimuli were administered to the volar surface of the forearm using a 30 mm X 30 mm thermode probe and a computer-controlled Medoc TSA-II Neuro Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). The thermode is a Peltier-element-based stimulator, with both heating and cooling capacity. For safety, in the present study the maximum temperature was set to 50°C while the minimum temperature was set to 0 C. If the temperature of the thermode reached either of these thresholds, it automatically
returned to baseline temperature (32°C). During thermal stimulation participants continuously rate pain intensity using a slider attached to a computerized numerical graphic rating scale with anchors of 0, “no pain” to 10, “pain as bad as it could be” (Turk & Melzak, 2001). Temperature data from the thermode and participant pain ratings were sampled at 100 Hz and recorded using TSA software version 5.35. If a participant provided a rating of 10, or “pain as bad as it could be,” the experimental trial was ended.

Procedure

Consent, Interview, and Initial Measures

After arriving in the laboratory, participants were given the opportunity to provide informed consent to all procedures. Following consent, participants received a questionnaire to assess adherence to the study restrictions and were asked to complete an interview (Structured Interview for Headaches) to clarify headache symptoms. Next, participants completed the Center for Epidemiologic Studies Depression Scale (CES-D), State Trait Anxiety Inventory (STAI), and Brief Pain Inventory (BPI). Assessment of baseline problematic alcohol use (Alcohol Use Disorders Identification Test; AUDIT), caffeine use (the Weekly Caffeine Intake Survey), sleep quality (the Pittsburgh Sleep Quality Index), stress level (the Perceived Stress Scale), and amount of exercise (the 7-day Physical Activity Recall Questionnaire) was conducted. After this, participant height and weight was measured using a stadiometer. Participants were then prepared for measurement of heat pain. Also in order to characterize the sample, systolic and diastolic blood pressure were measured using a Critikon, Dinamap Compact T electronic, oscillometric sphygmomanometer with the cuff placed over the non-dominant upper arm.
Heat Pain Threshold Assessment

Next, participants’ pain threshold for heat stimuli was determined. Heat stimuli were delivered to the ventral surface of the forearm. The thermode was placed on the skin of the forearm and then secured with a Velcro strip. Temperatures started at 32°C (which is a non-noxious temperature at which most participants report feeling neither cold nor warmth) and then increased at 0.5°C/s until pain threshold was reached. Participants clicked a mouse when the stimulation first became painful. Upon clicking the mouse, the temperature immediately returned to the non-noxious baseline level. Pain threshold was assessed three times with two minute breaks between trials and then averaged. If a participant reached the upper temperature limit (50°C) without indicating their pain threshold had been reached, the temperature automatically returned to the baseline level, and the temperature of 49°C was used for that trial. Next, blood pressure and heart rate were assessed for a second time.

Experimental Trials

Then, participants underwent three blocks of continuous heat stimuli rated using the thermode’s Computerized Visual Analog Scale (COVAS). Using a sliding bar, each stimulus was continually rated from 0 (no pain) to 10 (pain as bad as it could be). If at any time a participant gave a stimulation rating of 10, that trial was immediately terminated and participants were given the option of whether or not they wanted to continue the protocol. Each block of heat stimuli trials consisted of three types: offset, control, and constant temperature (see Figure 1). For offset trials, participants experienced 5s at their heat pain threshold (T1), then 5s at 1°C above this temperature
(T2), and then 20s at the initial T1 temperature (T3). During control trials, T1 and T2 were identical to experimental trials, but the temperature during the 20s of T3 dropped to 32°C. Constant temperature trials consisted of 30s at the T1 temperature. The stimulation order was the same for each participant: block one was experimental, constant, control; block two was constant, control, experimental; and block three was control, experimental, constant. Rate of temperature change during experimental and control trials was 6°C/s. Participants received a 2 minute break between each type of trial.

**Final Measures and Debriefing**

At the conclusion of the third block of heat stimuli, retrospective pain ratings about the experimental stimuli were assessed with the McGill Pain Questionnaire (MPQ) and stimulus pain-related anxiety was measured with the Situational Catastrophizing Questionnaire (SCQ). The Pain Catastrophizing Scale (PCS) and the Pain Anxiety Symptoms Scales (PASS) were completed, and blood pressure and heart rate were assessed a third time. Finally the debriefing form was reviewed with the participants, and they were given an opportunity to ask questions and request a summary of their physiological responses.

**Data Analysis**

Primary analyses included two methods of determining the presence of offset analgesia (OA1; OA2) and comparing the magnitude of offset analgesia between participants with tension-type headaches, migraine headaches, and healthy controls. The principle method of assessing offset analgesia (OA1) was conducted using a paired-samples t-test to determine if the magnitude of the change in pain rating from T1 to T2
(ΔT1:T2) was significantly different from the magnitude of the change in pain rating from T2 to T3 (ΔT2:T3; see Figure 1). Next, it was established that the decreased pain rating in the offset trials was not due to the natural reduction in pain perception that occurs in response to experiencing the same stimulus over time (habituation). To make this determination, a t-test was conducted to compare the mean of the lowest pain rating during T3 of the offset trials to the mean of the pain rating at the same time point during T3 of the constant trials.

To compare the magnitude of offset analgesia across sample groups, a mixed between (Tension-type, Migraine, Healthy Controls)-within (ΔT1:T2, ΔT2:T3) analysis of variance (ANOVA) was conducted, with offset analgesia defined as stated above (OA1; ΔT1:T2 to ΔT2:T3). This was followed by a second mixed between (Headache, Healthy Control)-within (ΔT1:T2, ΔT2:T3) ANOVA that compared all participants with headaches too frequent to meet criteria for the healthy control group (including 9 participants with mixed or unclear headaches) to those participants in the healthy control group (see Figure 2).

Next, the relationship between the magnitude of offset analgesia (OA1) and headache frequency was determined. The variable “headache frequency” was positively skewed. In order to reduce positive skew and more accurately capture the relationship between headache frequency and magnitude of offset analgesia, participants who met criteria for the healthy control group (n = 24) were excluded from this analysis. Additionally, for ease of presentation and to facilitate the use of non-parametric analysis, offset analgesia was calculated as a difference score (ΔT1:T2-ΔT2:T3). A Kendall’s tau
non-parametric correlation test was conducted to assess the relationship between headache frequency and degree of offset analgesia (OA1; see Figure 4).

As previously stated, offset analgesia has been operationalized and assessed using a variety of methods. In the second method of quantifying the magnitude of offset analgesia (OA2), the value of the difference between the highest pain rating during the second test period (T2) and the lowest pain rating during the third test period (T3) divided by the highest pain rating during T2 was established (ΔT2-T3/T2; see Figure 1; see Figure 5). Offset analgesia is said to be present when ΔT2-T3/T2 is greater in the offset trials than in the constant trials. This value (ΔT2-T3/T2) in the offset trials was compared to the same value in the constant trials using a paired-samples t-test. Next, these values were compared across sample groups using a mixed between (Tension-type, Migraine, Healthy Control)-within (ΔT2-T3/T2\textsubscript{offset}, ΔT2-T3/T2\textsubscript{constant}) ANOVA. Following this, the relationship between the magnitude of this method of calculating offset analgesia (OA2) and headache frequency was determined. Again, due to the positive skew in the distribution of headache frequency, the healthy control group was removed from the analysis (n = 24) and the magnitude of offset analgesia (OA2) was calculated as a difference score (ΔT2-T3/T2\textsubscript{offset} - ΔT2-T3/T2\textsubscript{constant}). Kendall’s tau correlation test was conducted to determine the relationship between headache frequency and OA2.

The participant groups (Tension-type, Migraine, and Healthy Control) were compared across a variety of demographic, physiological, and psychosocial measures in order to characterize the sample and investigate potential confounds. Gender, race,
ethnicity, and completion of temperature trial data were investigated using chi-square analyses. The Kruksal-Wallis test was used to compare variables with a significant non-normal distribution (CESD, PASS, PSS, BPI severity, BPI interference, and McGill Pain Questionnaire) across the participant groups, while traditional analysis of variance (ANOVA) was used to compare all other sample characteristics across groups. Participant gender, age, and race were initially included as between-subjects variables; however, these effects were non-significant in all analyses and were therefore not included in final models. Post-hoc analyses were conducted for significant omnibus tests using Tukey’s method to control for familywise error. A $p$ value of less than .05 was considered statistically significant. Data from the Control trials (see Figure 1) were not examined in the current study due to their irrelevance to the two primary methods of calculating offset analgesia.

In summary, participant flow and a thorough examination of participant characteristics will be provided. After that, information about participant heat pain threshold and the primary outcomes of the study are presented. Primary outcomes included two methods of determining the presence of offset analgesia (OA1 and OA2) and comparing the magnitude of offset analgesia between participants with tension-type headaches, migraine headaches, and healthy controls. Finally, the relationship between headache frequency and the magnitude of offset analgesia (OA1 and OA2) are presented.
RESULTS

Participant Flow

For an overview of the flow of participants through each stage of the study, see Figure 2. Of the 111 participants who signed up for the study and attended the appointment time, 7 participants were excluded prior to participating in the temperature trials. One participant became ill and left before completing the study and 6 participants did not meet the screening criteria (1 participant had alcohol within 4 hours of the study, 2 participants had smoked within an hour of the study, 2 participants had comorbid health conditions, and 1 participant had caffeine within 4 hours of the study). Of those participants who met screening criteria but did not complete the study, 2 participants discontinued the study due to discomfort and 2 participants maxed out their pain rating during three or more trials and were excluded. Eight participants maxed out their pain rating during one or two temperature trials and their missing data were replaced with the average of other similar trials (i.e. offset, constant).

For the analyses, different sections of the sample were used. All summary statistics included the full sample of participants who completed the study \((n = 100)\). For most analyses comparing sample groups, only those participants who met criteria for the tension-type, migraine, or healthy control groups were included \((n = 91)\). For analyses related to headache frequency, all participants with headaches too frequent to qualify for the healthy control group \((n = 76)\) were included.
Sample Characteristics

*Headache Characteristics*

Of the 100 participants retained in the final analyses, 24 met the criteria for the healthy control group, 27 met criteria for episodic migraine headache, 40 met criteria for tension-type headache (9 infrequent episodic, 30 frequent episodic, 1 chronic), 7 met criteria for more than one headache group, and 2 did not meet criteria for any group. For most analyses comparing sample groups, only those 91 participants who met criteria for the tension-type, migraine, or healthy control group were included. Headache frequency varied widely among the 76 participants whose headaches were too frequent to be included in the healthy control group, from 9 to 365 headaches ($M = 52.7$, $SD = 65.2$). These 76 participants were included in analyses examining the relationship between headache frequency and the magnitude of offset analgesia.

Levels of headache disability, as measured by the headache disability index (HDI), significantly differed between the groups, $F (2, 88) = 8.65, p < 0.01$. Participants in the migraine group ($M = 26.2$, $SD = 17.5$) had significantly higher levels of self-reported headache disability than either the tension-type ($M = 11.6$, $SD = 11.8$) or healthy control groups ($M = 11.8$, $SD = 17.7$). Additionally, participants in the migraine group had higher levels of self-reported headache pain severity as measured by both the BPI and the BSQ than the tension-type or healthy control groups ($H (2) = 9.13, p = 0.01$; $H (2) = 24.53, p < 0.001$). While participants’ self-reported pain interference did not reach
significance, this is likely due to the higher level of variability in pain interference than in pain severity, as the levels of the measures were very similar (see Table 1).

**Demographic Characteristics**

Participants were aged between 18 and 25 ($M = 19.3$, $SD = 1.4$, $n = 100$). The healthy control group ($M = 20.0$, $SD = 1.6$) was slightly older than the migraine ($M = 19.1$, $SD = 1.5$) and tension-type groups ($M = 19.3$, $SD = 1.0$; $H(2) = 6.88$, $p = 0.03$; see Table 1).

While most of the sample was Caucasian ($n = 80$), 14 participants identified as Asian/Pacific Islander and 6 participants identified as Black or African American (see Table 1). Three participants identified as having Hispanic ethnicity. The groups varied by race: participants who identified as Asian or Pacific Islander (50%) or Black or African American (75%) were more likely to meet criteria for the healthy control group than the participants identifying as White (19.2%). Participants identifying as White (52.1%) were more likely to meet criteria for the tension-type group than participants identifying as Asian or Pacific Islander (14%) or Black or African American (0.0%), $\chi^2(2, 91) = 13.86$, $p = 0.01$. There were no statistically significant differences in ethnicity between the groups, $\chi^2(2, 91) = 4.85$, $p = 0.09$, although this analysis was underpowered.

Participants were 46 men and 54 women. Consistent with previous research, the migraine group had the highest percentage of women (81.5%). In this sample, the healthy control group had a higher proportion of male participants than the other groups, $\chi^2(2, 91) = 14.74$, $p < 0.01$ (see Table 1).
Physiological Characteristics

Participants’ systolic and diastolic blood pressure did not vary by participant group at baseline ($F(2, 89) = 2.71, p = 0.07; F(2, 89) = 0.42, p = 0.66$, respectively). As a whole, participants’ average systolic blood pressure decreased from time 2 (T2) to time 3 (T3), $t(99) = -2.58, p = 0.01$ (see Table 1). However, there were no significant differences in average systolic or diastolic blood pressure between the sample groups. Groups also did not significantly differ in terms of Body Mass Index (BMI), weekly caffeine intake, physical activity, sleep, or problematic alcohol use (see Table 1).

Psychosocial Characteristics

The participant groups did not differ in two measures of how they experienced the experimental stimuli (Situational Catastrophizing Questionnaire; McGill Pain Questionnaire). Participants in the migraine group ($M = 31.9, SD = 12.8$) had significantly higher levels of pain anxiety than the tension-type ($M = 23.4, SD = 13.2$) or healthy control groups ($M = 23.2, SD = 14.4; H(2) = 7.40, p = 0.03$). Trait levels of anxiety, depression, perceived stress, and pain catastrophizing did not differ between the three groups (see Table 1).

Examination of Offset Analgesia

Pain Threshold

The average heat pain threshold for the full sample was $44.4 \, ^\circ\text{C} \ (SD = 2.6)$. A one-way ANOVA (Tension-type, Migraine, Healthy Control) was conducted to examine heat pain threshold across the three groups. Results indicated that there was no significant
difference across the tension-type ($M = 44.1 \degree C, SD = 2.9$), migraine ($M = 44.5 \degree C, SD = 2.5$), or healthy control groups, ($M = 44.6 \degree C, SD = 2.2$), $F(2, 88) = 0.29, p = 0.75$.

**Offset Analgesia Calculation 1 (OA1)**

The primary outcomes of the study were an examination of the magnitude of offset analgesia and a comparison of the magnitude of offset analgesia across groups. The principal method of calculating offset analgesia (OA1) was a paired-samples t-test comparing the magnitude of the increase in pain rating from T1 to T2 ($M = 10.8, SD = 6.8$) to the decrease in pain rating from T2 to T3 ($M = 15.1, SD = 12.7$). As can be seen in Table 2 and Figure 3, as a whole participants demonstrated the offset analgesia effect—a disproportionately large decrease in pain ratings relative to a small decrease in stimulus temperature, $t(99) = 3.54, p < 0.01, d = 0.35$. Additionally, the magnitude of offset analgesia was compared to habituation, or the natural reduction in pain perception that occurs in response to experiencing the same stimulus over time. This comparison of the mean of the lowest pain rating during T3 of the offset trials ($M = 13.7, SD = 12.6$) to T3 at the same time point of the constant trials ($M = 23.1, SD = 16.5$) was significant, $t(99) = -8.54, p < 0.01, d = 0.85$, indicating that the decrease in pain rating during T3 of the offset trials cannot be attributed to habituation.

A mixed between (Tension-type, Migraine, Healthy Control)-within ($\Delta T1:T2$, $\Delta T2:T3$) ANOVA was conducted to compare the magnitude of offset analgesia across the three groups. While it was predicted that the degree of offset analgesia in both the tension-type ($M_{\Delta T1:T2} = 10.0, SD = 6.5; M_{\Delta T2:T3} = 16.1, SD = 13.5$) and migraine ($M_{\Delta T1:T2} = 10.8, SD = 6.9; M_{\Delta T2:T3} = 15.8, SD = 12.9$) groups would be significantly reduced in
comparison to the healthy control group ($M_{\Delta T1:T2} = 13.2, SD = 7.7$; $M_{\Delta T2:T3} = 15.5, SD = 12.8$), there was no statistically significant interaction between participant group and section of trial, $F(2, 88) = 1.17, p = 0.31, \eta_p^2 = .026$. There was a significant main effect for section of trial, $F(1, 89) = 9.38, p < 0.01, \eta_p^2 = .096$, with a greater magnitude of reduction in pain rating from T2 to T3 than increase in pain rating from T1 to T2 in the offset trials (see above), consistent with the offset analgesia effect. The main effect of participant group was not significant, $F(2, 88) = 0.1, p = 0.92, \eta_p^2 = .002$, suggesting no statistically significant difference in the magnitude of either the increase in pain rating from T1 to T2 or the decrease from T2 to T3 across participant groups (see Table 2 and Figure 3).

Next, all participants with headaches too frequent to be included in the healthy control group ($n = 76$, including 9 participants who did not meet criteria for the tension-type or migraine groups) were compared to the healthy control group ($n = 24$) using a mixed between (Headache, Healthy Control)-within (ΔT1:T2, ΔT2:T3) ANOVA. Again, the interaction between section of trial and participant group was not statistically significant, $F(1, 89) = 2.01, p = 0.16, \eta_p^2 = .024$. There was a significant main effect for section of trial, $F(1, 89) = 5.31, p = 0.02, \eta_p^2 = .058$, with a greater magnitude of ΔT2:T3 in the offset trials. The main effect comparing the two participant groups was not significant, $F(1, 89) = 0.41, p = 0.53, \eta_p^2 = .002$, indicating no statistically significant difference in the magnitude of either ΔT2:T3 or ΔT1:T2 between the participant groups.

It was also proposed that the magnitude of offset analgesia may be reduced as headache frequency increases. In order to reduce the positive skew in the variable
“headache frequency” and more accurately capture the relationship between headache frequency and magnitude of offset analgesia, participants who met criteria for the healthy control group \((n = 24)\) were excluded from this analysis. As examined by a Kolmogorov-Smirnov test, headache frequency remained significantly positively skewed, \(D (76) = .32, p < .001\). For ease of presentation and to facilitate the use of non-parametric analysis, offset analgesia was calculated as a difference score, \((\Delta T1:T2-\Delta T2:T3)\). A Kendall’s tau non-parametric correlation test was conducted to assess the relationship between headache frequency and degree of offset analgesia, and no statistically significant relationship was found between the two variables, \(\tau (76) = .004, p = .96, d = 0.01\) (see Figure 4).

**Offset Analgesia Calculation 2 (OA2)**

In order to be consistent with previous research, a second alternative method of assessing offset analgesia was also conducted. In this OA2 calculation method, the difference between the highest pain rating during the second test period and the lowest pain rating during the third test period was divided by the highest pain rating during the second test period (i.e., \(\Delta T2-T3/T2\)). Offset analgesia is said to be present when \(\Delta T2-T3/T2\) is greater in the offset trials \((M = 0.70, SD = 0.25)\) than in the constant trials \((M = 0.53, SD = 0.29)\). As can be seen in Table 2, and consistent with the presence of an offset analgesia effect, this hypothesis was supported for the overall sample, \(t (99) = 7.53, p < 0.01, d = 0.75\).

A mixed between (Tension-type, Migraine, Healthy Control)-within (\(\Delta T2-T3/T2_{\text{offset}}, \Delta T2-T3/T2_{\text{constant}}\)) ANOVA was conducted to examine offset analgesia across
the three participant groups. While it was predicted that the degree of offset analgesia in both tension-type ($M_{\Delta T2-T3/T2}^{\text{offset}} = 0.71, SD = 0.24; M_{\Delta T2-T3/T2}^{\text{constant}} = 0.54, SD = 0.25$) and migraine ($M_{\Delta T2-T3/T2}^{\text{offset}} = 0.76, SD = 0.20; M_{\Delta T2-T3/T2}^{\text{constant}} = 0.57, SD = 0.32$) would be significantly reduced in comparison to the healthy control group ($M_{\Delta T2-T3/T2}^{\text{offset}} = 0.64, SD = 0.27; M_{\Delta T2-T3/T2}^{\text{constant}} = 0.52, SD = 0.32$), there was no statistically significant interaction between participant group and type of trial, $F(2, 88) = 0.61, p = 0.55, \eta^2_p = .014$ (see Table 2 and Figure 5). This indicates that there was no difference between participant groups in the magnitude of the difference between $\Delta T2-T3/T2^{\text{offset}}$ and $\Delta T2-T3/T2^{\text{constant}}$. There was a significant main effect for type of trial, $F(1, 89) = 42.13, p < 0.01, \eta^2_p = .324$, with $\Delta T2-T3/T2^{\text{offset}}$ greater than $\Delta T2-T3/T2^{\text{constant}}$. The main effect comparing the three participant groups was not significant, $F(2, 88) = 0.72, p = 0.49, \eta^2_p = .016$, indicating that the groups did not differ in either $\Delta T2-T3/T2^{\text{offset}}$ or $\Delta T2-T3/T2^{\text{constant}}$ (see Table 2).

Next, all participants with headaches too frequent to be included in the healthy control group ($n = 76$, including 9 participants who did not meet criteria for the tension-type or migraine groups) were compared to the healthy controls ($n = 24$) using a mixed between (Headache, Healthy Control)-within ($\Delta T2-T3/T2^{\text{offset}}, \Delta T2-T3/T2^{\text{constant}}$) ANOVA. There was no statistically significant interaction between participant group and type of trial, $F(1, 98) = 1.34, p = 0.25, \eta^2_p = .012$, indicating that there was no difference by participant group in the magnitude of the difference between $\Delta T2-T3/T2^{\text{offset}}$ and $\Delta T2-T3/T2^{\text{constant}}$. There was a significant main effect for type of trial, $F(1, 98) = 34.16, p < 0.01, \eta^2_p = .253$, with a greater magnitude of $\Delta T2-T3/T2^{\text{offset}}$ than $\Delta T2-T3/T2^{\text{constant}}$. The
main effect comparing the two participant groups was not significant, $F (1, 98) = 0.55, p = 0.46, \eta_p^2 = .011$, indicating that the groups did not differ either $\Delta T_2-T_3/T_{2\text{offset}}$ or $\Delta T_2-T_3/T_{2\text{constant}}$.

Finally, the relationship between this method of calculating offset analgesia (OA2) and headache frequency was examined. As with the first method of calculating offset analgesia (OA1), in order to reduce the positive skew in the data and more accurately capture the relationship between headache frequency and magnitude of offset analgesia, participants who met criteria for the healthy control group ($n = 24$) were excluded from the analysis. Again, for ease of presentation and to facilitate the use of non-parametric analysis, offset analgesia was calculated as a difference score, $(\Delta T_2-T_3/T_{2\text{offset}} - \Delta T_2-T_3/T_{2\text{constant}})$. As can be seen in Figure 6, a Kendall’s tau non-parametric correlation test revealed that the relationship between headache frequency ($M = 52.7, SD = 65.2$) and degree of offset analgesia (OA2; $M = 0.2, SD = 0.2$) was not significant, $\Upsilon (76) = -0.15, p = 0.07, d = .30$. 


DISCUSSION

The present study sought to compare offset analgesia in participants with tension-type headache, migraine headache, and healthy controls. Several important contributions emerged from these data. First, offset analgesia has never been examined in individuals with migraine or tension-type headache. Second, in contrast to predictions, the degree of offset analgesia did not differ between those participants with migraine headaches, tension-type headaches, and healthy controls. Finally, also in contrast to predictions, the degree of offset analgesia was not significantly correlated with headache frequency. What follows is a review of primary outcomes, followed by limitations and future directions.

Offset Analgesia

As predicted, the offset analgesia (OA) effect was present in the full sample. OA has been demonstrated to be a powerful effect present across gender and age groups, and has recently been shown to be easily reproduced within and across measurement days (Niesters, et al., 2011b; Nilsson et al., 2014). However, aside from the work conducted by Niesters and colleagues (2001b), OA has only been assessed in pain-free participants. While participants in the current study were not severely impaired, the majority of participants reported symptoms significant enough to meet criteria for tension-type or migraine headache. Therefore, this is the first study to demonstrate unaltered offset analgesia in a sample of participants with pain concerns, providing further evidence of the robust effect of OA across groups.

Previously, offset analgesia has been assessed using multiple methods. In the current study there was a significant OA effect in the full sample as assessed with both of
the two most commonly utilized methods of calculation: OA1 and OA2. As further illustration of the strength of the OA effect, both methods of calculation included a comparison demonstrating that the OA effect is greater than the reduction in pain rating expected due to habituation. However, in the present sample the OA effect appeared to have a smaller magnitude than in previous studies (i.e. Grill & Coghill, 2002; Yelle, Rogers, & Coghill, 2008). This may be related to the use of individualized test temperatures, in contrast to earlier studies utilizing the 49:50:40°C procedure. Although the average test temperature in the current study (44.3°C) was similar to stimulus intensities in other studies of OA (i.e. Derbyshire & Osborn, 2008; 2009; Niesters et al., 2011b), it has been established that the magnitude of offset analgesia is reduced at lower test temperatures (Derbyshire & Osborn, 2008; 2009). While it is tempting to attribute the lower magnitude of offset analgesia in the current sample to the inclusion of participants with headache concerns, as this would support the hypothesized impairment of pain modulation, this is not a viable explanation for two reasons. First, there was no statistically significant difference in the magnitude of OA between the three groups, and second, OA1 was statistically significant in the headache groups but not in the healthy control group. While participants in the healthy control group did demonstrate a larger decrease in pain rating from T2 to T3 than increase from T1 to T2 in the offset trials, this difference did not reach statistical significance. This is likely attributable to the healthy control group’s larger (although not statistically significant) reaction to the increase in temperature from T1 to T2. The healthy control group’s greater magnitude in pain rating increase is surprising given that there were no other indications of a difference in pain
perception; there were no statistically significant differences between the groups in heat pain threshold or pain-related participant characteristics. When an alternative method of calculating offset analgesia was utilized (i.e., OA2), offset analgesia in the healthy control group was statistically significant and similar in magnitude to the other two participant groups. Therefore, OA2 may be the preferred technique for calculating offset analgesia as it corrects for the magnitude of the increase from T1 to T2.

Comparison of Offset Analgesia across Participant Groups

In contrast to predictions, the magnitude of offset analgesia did not differ significantly between the three sample groups: participants with migraine headache, participants with tension-type headache, and healthy controls. This is inconsistent with the findings of the only previous study to examine OA among individuals with chronic pain (Niesters et al., 2011b), in which it was demonstrated that OA was reduced or absent in a sample of patients with neuropathic pain. The absence of group differences in OA was also unexpected in that there is a wealth of existing data demonstrating altered central pain processing in individuals with tension-type and migraine headaches (i.e. Ashina et al., 2006; Ashina et al., 2005; Burstein et al., 2000; Cathcart et al., 2010; Coppolla et al., 2010; Fernandez-de-Las-Penas et al., 2007; Goadsby, 2012; Gobel et al., 1992; Lous & Olesen, 1982; Pielsticker, Haag, Zaudig, & Lautenbacher, 2005; Sandrini et al., 2006). It should be noted, however, that the majority of the existing studies that have demonstrated altered central pain processing were conducted with chronic headache patients. There are few studies that have included participants who are more comparable to the current sample based on milder headache symptoms, and these typically failed to
find altered pain perception in participants with episodic headaches (i.e. Leon-Sarmiento, Schroeder, & Ruiz, 2008), or have found that the magnitude of the alteration in pain processing fell somewhere between the group of healthy controls and the group of chronic headache suffers (i.e. Buchgreitz et al., 2008a; Buchgreitz, Lyngberg, Bendtsen, & Jensen, 2006; Wallasch, Reinecke, Langhor, 1991). Thus, while it is possible to conclude from the present data that OA is not impacted in individuals with the two most common forms of headache, it is also possible that OA would be altered in clinical samples with greater headache frequency, severity, or chronicity. Consistent with this notion, there is evidence that the duration and severity of headache disorders are related to the likelihood of developing central pain processing changes. For example, decreased pressure pain and cold detection thresholds at extracephalic sites (i.e. ankle, arm) have been related to the frequency of headache episodes in individuals with tension-type headaches (Fernandez–de-Las-Penas et al., 2007; Schoenen, Bottin, Hardy, & Gerard, 1991; Schoenen, Hardy, & Gerard, 1983). Additionally, Buchgreitz and colleagues (2006; 2008b) examined participants’ pressure pain thresholds and pericranial muscle tenderness at baseline and 12-year follow-up. The authors found that participants with normal baseline thresholds and tenderness had decreased thresholds and higher levels of tenderness at follow-up if they developed either frequent episodic tension-type headache or chronic tension-type headache. The authors concluded that pressure pain sensitivity and muscle tenderness are a consequence rather than a cause of frequent tension-type headache, and emphasized the importance of the role of central sensitization in the chronification of headache. Finally, a longitudinal study conducted by Scher and
colleagues (2003) examined risk factors for the development of chronic daily headache. Individuals with both migraine and tension-type headaches were interviewed at baseline and again approximately 11 months later. At baseline, the selected participants had between 2 and 104 headaches per year. While the large majority (91%) of the sample was stable over the follow-up period, 6% of participants went on to develop intermediate chronic daily headache (105-179 headaches per year) and 3% developed chronic daily headache. Having at least one attack per week (52 headaches per year) was significantly predictive of developing both intermediate and chronic daily headache, providing further evidence that headache frequency contributes to the chronification of headache. Finally, in comparison to the only study in which OA has been demonstrated to be significantly reduced in a clinical pain sample (Niesters et al., 2011b), participants in the current study had a relatively low level of pain and disability. For example, current study participants in the migraine group had the highest levels of headache severity and headache-related disability, but these levels were still particularly low in comparison to clinical populations (Sauro & Becker 2008; Hamdy, Samir, El-Sayed, Adel, & Hasan, 2008). Additionally, there was little evidence that the level of headaches experienced by current participants had a significant impact on their psychosocial functioning as indicated by a lack of group differences in reported anxiety, depression, or stress; measures that have previously been shown to be correlated with chronic headaches (i.e. Heckman & Holroyd, 2006; Sheftell & Atlas, 2002). In combination with evidence suggesting that alterations in pain modulation may be related to headache chronification and the low levels of clinical severity in the current sample, the absence of a significant difference in
the magnitude of OA between the participant groups may indicate that OA represents a form of descending pain inhibition that is only attenuated in individuals with chronic pain.

Strengths, Limitations, and Directions for Future Research

The present study had a number of important strengths. Participants were carefully screened for suitability, and were assessed with a wide variety of psychosocial and biological measures. Participants’ headache characteristics were thoroughly investigated using both a questionnaire and extensive interview, enabling the recruitment of two headache groups as well as controls. Individual test temperatures were utilized, ensuring that the procedure was delivered at a level of intensity appropriate for each participant. Participants were asked about their experience of the trial stimuli, providing a form of manipulation check. Finally, OA was assessed using multiple methods, allowing for the evaluation of these methods in comparison to each other.

In addition to these important strengths, several limitations must also be noted when interpreting the results. For example, there was no statistically significant relationship between OA and headache frequency. This may be partially related to a “floor effect” in headache frequency. Over 50% of participants had 18 or fewer headaches per year. This number of headaches meets the frequency criteria for both episodic migraine and frequent episodic tension-type headache diagnoses, but only 8 participants had a sufficient frequency of headaches to meet the criterion for “chronic” headaches (>150 headaches/year). While the current study indicates there is no relationship between headache frequency and OA at a low level of frequency, there is
evidence described above that alterations in central pain processing may occur only at higher levels of headache frequency and duration of illness (Buchgreitz et al., 2006; Fernandez–de-Las-Penas et al., 2007; Scher et al., 2003; Schoenen et al., 1983). The nature of the non-clinical sample is not the only potential limitation of the current study, as will be described below.

Fewer individuals who met criteria for the healthy control group participated than expected. This may have been due to a sampling bias. The materials provided to the pool of potential participants included a description of the study. The word “headache” was in the title, and it was clear that participants would be asked about their headache history. This may have drawn participants to the study with more frequent headaches, and could be controlled in future investigations through the use of more neutral language such as, “examination of heat stimuli.” Additionally, individuals tend to overestimate headache frequency when asked for a retrospective recollection (e.g., Schwarz, 2004). This may have led some participants to over-report headache frequency and be included in one of the headache groups when they belonged in the healthy control group. The use of a headache diary that includes information about headache frequency and severity would potentially increase the accuracy of headache classification (Holroyd, 2002; McKenzie & Cutrer, 2009). Furthermore, consistent with prior research, the demographic characteristics of the participants, particularly gender, varied considerably by sample group (i.e. migraine, tension-type, and healthy control). While these characteristics did not significantly alter the outcomes of the study when included in statistical models, previous work has demonstrated a significant relationship between gender, chronic pain,
and the clinical characteristics associated with chronic pain (Celentano, Linet, & Stewart, 1990; Mitsikostas & Thomas, 1999). Therefore, future studies may benefit from either gender matching or including only female participants. Finally, in the present study the experimenter who interviewed participants about headache characteristics also conducted the trials of heat stimuli. While there are potential benefits of utilizing the same experimenter for both stages, such as increased participant comfort, it also raises the possibility of experimenter bias. In order to reduce potential experimenter bias, the experimenter who is conducting the heat stimuli trial procedures should be blinded to the headache characteristics of the participant.

With the aforementioned strengths and weaknesses in mind, the current findings suggest several areas for future investigation. One potentially fruitful design change would be to investigate OA in individuals with headache concerns utilizing more intense stimuli. Suprathreshold testing has been shown to be more reliable in demonstrating altered pain processing in individuals with headache disorders (Bendtsen, Jensen, & Olesen, 1996; Jensen, Bendtsen, & Olesen, 1998; Schoenen et al., 1991). In combination with the greater magnitude of OA at higher temperatures, it may be beneficial to utilize “high pain” rather than “pain threshold” stimuli. Additionally, OA has only been examined with heat stimuli. Due to the relevance of pressure pain to headache disorders, particularly tension-type headaches, it would be interesting to investigate OA using pressure in addition to heat stimuli. Finally, while the findings of the current study were contrary to what was expected, given further investigation involving clinical populations of participants with chronic headache disorders OA may be able to be used to assess the
transition from episodic to chronic headaches (Derbyshire & Osborn, 2009). For example, OA, a relatively time-efficient methodology, could be used for repeated testing over time in order to allow for the identification of the level of severity at which central processing begins to be impacted. Increased clarification of the process of chronification could enable providers to tailor their interventions more specifically, and thereby reduce the burden of headaches on the individual and society. Further, a second measure of pain processing such as conditioned pain modulation could be added. Conditioned pain modulation has been shown to be altered in individuals with chronic headaches (Coppola et al., 2010; Pielsticker et al., 2005; Sandrini et al., 2006). Therefore, with the longitudinal design described above, OA could be examined as a potential indicator of the development of central dysfunction while being compared to a measure of endogenous pain modulation that has already been shown to be impacted in individuals with chronic but not episodic headaches.

In sum, the results of the current study demonstrated offset analgesia in a sample of young adults, and provided initial evidence that this form of descending pain modulation is not impaired in high-functioning young adults with relatively mild headache symptoms. However, these findings do not rule out the possibility that OA differences may be observed among those with more severe or more prolonged headache symptoms, and a longitudinal investigation of the relationship between headache chronification and possible alterations in OA would shed new light on the role of central pain processing in chronic headache disorders.
REFERENCES


Table 1

Sample characteristics by participant group

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Tension-type</th>
<th>Migraine</th>
<th>Healthy Control</th>
<th>Three Group Sample&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Sample&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 27</td>
<td>n = 24</td>
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<td>HA Freq.*</td>
<td>37.4 (45.3)</td>
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<td>White 58.3%</td>
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<tr>
<td>Women</td>
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<td>Syst. BP</td>
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<td>(624.7)</td>
<td>(372.6)</td>
<td>(532.6)</td>
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<td>Audit</td>
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**Psychosocial Characteristics**

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<td>1.9 (3.0)</td>
<td>1.5 (2.2)</td>
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<td>7.3 (6.9)</td>
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<td>Pain Anxiety*</td>
<td>23.4 (13.2)</td>
<td>31.9 (12.8)</td>
<td>23.2 (14.4)</td>
<td>25.9 (13.8)</td>
<td>25.0 (13.7)</td>
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<td>STAI trait</td>
<td>38.0 (8.4)</td>
<td>41.6 (10.8)</td>
<td>36.6 (9.4)</td>
<td>38.7 (9.4)</td>
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<td>CESD-R</td>
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<td>14.6 (9.1)</td>
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<td>Stress</td>
<td>10.1 (4.2)</td>
<td>12.5 (4.9)</td>
<td>10.0 (5.4)</td>
<td>10.8 (4.8)</td>
<td>10.7 (4.7)</td>
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<td>Trait Cat.</td>
<td>9.3 (7.4)</td>
<td>11.9 (7.2)</td>
<td>8.8 (7.3)</td>
<td>9.9 (7.3)</td>
<td>9.8 (7.2)</td>
</tr>
</tbody>
</table>

* Participants who met criteria for the Tension-type, Migraine, or Healthy Control Groups
b All participants, including those who had mixed headaches or did not meet criteria for any group

Abbreviations: HA freq.=number of headaches per year as measured by the SDIH; HA sev.=headache severity as measured by the BSQ; HDI = Headache Disability Inventory; BPI = Brief Pain Inventory for headaches; Syst. BP = systolic blood pressure; Diast. BP = diastolic blood pressure; BMI = body mass index; Caffeine = Weekly Caffeine Intake; Phys. Act. = Physical Activity; PSQI = Pittsburg Sleep Quality Index; Sit. Cat. = Situational Catastrophizing Scale; Pain Anxiety = Pain Anxiety Symptom Survey; CESD-R = Center for Epidemiologic Studies Depression Scale-Revised; Stress = Perceived Stress Survey; Trait Cat. = Pain Catastrophizing Scale.

* = $p < 0.05$
Table 2

*Offset analgesia means and standard deviations by participant group*

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Tension-type Headache</th>
<th>Migraine Headache</th>
<th>Healthy Control</th>
<th>Three Group Sample&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Sample&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 27</td>
<td>n = 24</td>
<td>n = 91</td>
<td>n = 100</td>
</tr>
<tr>
<td>ΔT1:T2</td>
<td>10.0 (6.5)</td>
<td>10.8 (6.9)</td>
<td>13.2 (7.7)</td>
<td>11.1 (7.0)</td>
<td>10.8 (6.8)</td>
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<tr>
<td>ΔT2:T3</td>
<td>16.1 (13.5)</td>
<td>15.6 (12.9)</td>
<td>14.5 (12.0)</td>
<td>15.5 (12.8)</td>
<td>15.1 (12.7)</td>
</tr>
<tr>
<td>Difference score</td>
<td>6.1 (12.8)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>4.8 (12.8)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.3 (11.1)</td>
<td>4.5 (12.4)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>4.5 (12.4)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ΔT2-T3/T2 constant</td>
<td>0.54 (0.25)</td>
<td>0.57 (0.32)</td>
<td>0.52 (0.32)</td>
<td>0.54 (0.29)</td>
<td>0.53 (0.29)</td>
</tr>
<tr>
<td>ΔT2-T3/T2 offset</td>
<td>0.71 (0.24)</td>
<td>0.76 (0.20)</td>
<td>0.64 (0.27)</td>
<td>0.71 (0.24)</td>
<td>0.70 (0.25)</td>
</tr>
<tr>
<td>Difference score</td>
<td>0.17 (0.17)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.19 (0.29)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.12 (0.25)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.17 (0.23)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.17 (0.24)&lt;sup&gt;*&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Participants who met criteria for the Tension-type, Migraine, or Healthy Control Groups
<sup>b</sup> All participants, including those who had mixed headaches or did not meet criteria for any group

<sup>*</sup>= p < 0.05
Figure 1. Typical offset analgesia paradigm with stimulus temperature at test phase 1 (T1), test phase 2 (T2), and test phase 3 (T3) for experimental, control, and constant trials.
Figure 2. Study design flowchart
Figure 3. Mean magnitude of offset analgesia (OA1; ∆T2:T3-∆T1:T2) ± standard error of the mean by participant group
Figure 4. Relationship between mean magnitude of offset analgesia (OA1, ΔT2:T3-ΔT1:T2) and headache frequency with the healthy control group (n = 24) excluded
Figure 5. Mean magnitude of offset analgesia (OA2; ΔT2-T3/ΔT2 in the constant trials subtracted from ΔT2-T3/ΔT2 in the offset trials) ± standard error of the mean by participant group
Figure 6. Relationship between mean magnitude of supplemental offset analgesia (OA2; ΔT2-T3/ΔT2 in the constant trials subtracted from ΔT2-T3/ΔT2 in the offset trials) and headache frequency with the healthy control group (n = 24) excluded.
APPENDIX A: SUPPLEMENTAL METHOD OF CALCULATING OFFSET ANALGESIA

The second supplemental method for establishing offset analgesia (OA3) is the value of the difference between the highest pain rating during the second test period (T2) and the lowest pain rating during the third test period (T3; see Figure 1). Offset analgesia is said to be present when ΔT2-T3 is greater in the offset trials ($M = 32.2, SD = 16.0$) than in the constant trials ($M = 20.2, SD = 13.2$). This hypothesis was supported for the overall sample, $t(99) = 8.49, p < 0.01, d = 0.85$.

A mixed between (Tension-type, Migraine, Healthy Control)-within (ΔT2-T3 offset, ΔT2-T3 constant) ANOVA was conducted to examine offset analgesia across the three groups. While it was predicted that the degree of offset analgesia in both tension-type and migraine groups would be reduced in comparison to the healthy control group, there was no statistically significant interaction between participant group and type of trial, $F(2, 88) = 1.21, p = 0.30, \eta_p^2 = .027$. There was a significant main effect for type of trial, $F(1, 89) = 63.95, p < 0.01, \eta_p^2 = .421$, with a greater magnitude of reduction in pain rating from T2 to T3 in the offset trials than in the constant trials, consistent with the offset analgesia effect. The main effect of participant group was not significant, $F(2, 88) = 1.67, p = 0.19, \eta_p^2 = .037$, suggesting that the groups did not differ in either ΔT2-T3 offset or ΔT2-T3 constant (see Figure 8).

Next, all participants with headaches too frequent to be included in the healthy control group ($n = 76$, including 9 participants who did not meet criteria for the tension-type or migraine groups) were compared to the healthy controls ($n = 24$) using a mixed
between (Headache, Healthy Control)-within (ΔT2-T3\textsubscript{offset}, ΔT2-T3\textsubscript{constant}) ANOVA. There was no statistically significant interaction between participant group and type of trial, \( F(1, 98) = 0.48, p = 0.49, \eta^2_p = .008 \), indicating that there was no difference by participant group in the magnitude of the difference between ΔT2-T3\textsubscript{offset} and ΔT2-T3\textsubscript{constant}. There was a significant main effect for type of trial, \( F(1, 98) = 47.20, p < 0.01, \eta^2_p = .337 \), with a greater magnitude of reduction in pain rating from T2 to T3 in the offset trials than in the constant trials. The main effect comparing the two participant groups was not significant, \( F(1, 98) = 0.21, p = 0.65, \eta^2_p = .008 \), suggesting that the groups did not differ in the reduction in pain rating from T2 to T3 in either the offset trials or the constant trials.

Finally, the relationship between this method of calculating offset analgesia (OA3) and headache frequency was examined. As with the first and second methods of calculating offset analgesia (OA1, OA2), in order to reduce the positive skew in the data and more accurately capture the relationship between headache frequency and magnitude of offset analgesia, participants who met criteria for the healthy control group (\( n = 24 \)) were excluded from the analysis. Again, for ease of presentation and to facilitate the use of non-parametric analysis, offset analgesia was calculated as a difference score, (ΔT2-T3\textsubscript{offset} - ΔT2-T3\textsubscript{constant}). A Kendall’s tau non-parametric correlation test was conducted, and there was no statistically significant relationship between headache frequency (\( M = 52.7, SD = 65.2 \)) and degree of offset analgesia (OA3; \( M = 12.6, SD = 14.3 \)), \( \tau (76) = 0.03, p = 0.70, d = .06 \).
Figure 7. Mean magnitude of supplemental offset analgesia (OA3; ΔT2-T3 in the constant trials subtracted from ΔT2-T3 in the offset trials) ± standard error of the mean by participant group.
Figure 8. Relationship between mean magnitude of offset analgesia (OA3; ΔT2-T3 in the constant trials subtracted from ΔT2-T3 in the offset trials) and headache frequency with the healthy control group (n = 24) excluded.