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A randomized, placebo-controlled, double-blinded mechanistic clinical trial using endotoxin to evaluate the relationship between insomnia, inflammation, and affective disturbance on pain in older adults: A protocol for the sleep and Healthy Aging Research for pain (SHARE-P) study

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ABSTRACT

Chronic pain is prevalent in older adults. Treatment, especially with opioids, is often ineffective and poses considerable negative consequences in this population. To improve treatment, it is important to understand why older adults are at a heightened risk for developing chronic pain. Insomnia is a major modifiable risk factor for chronic pain that is ubiquitous among older adults. Insomnia can also lead to heightened systemic inflammation and affective disturbance, both of which may further exacerbate pain conditions in older adults. Endotoxin exposure can be used as an experimental model of systemic inflammation and affective disturbance. The current study aims to understand how insomnia status and endotoxin-induced changes in inflammation and affect (increased negative affect and decreased positive affect) may interact to impact pain facilitatory and inhibitory processes in older adults. Longitudinal data will also assess how pain processing, affective, and inflammatory responses to endotoxin may predict the development of pain and/or depressive symptoms. The current study is a randomized, double-blinded, placebo-controlled, mechanistic clinical trial in men and women, with and without insomnia, aged 50 years and older. Participants were randomized to either 0.8ng/kg endotoxin injection or saline placebo injection. Daily diaries were used to collect variables related to sleep, mood, and pain at two-week intervals during baseline and 3-, 6-, 9-, and 12-months post-injection. Primary outcomes during the experimental phase include conditioned pain modulation, temporal summation, and affective pain modulation ~5.5 hours after injection. Primary outcomes for longitudinal assessments are self-reported pain intensity and depressive symptoms. The current study uses endotoxin as an experimental model for pain. In doing so, it aims to extend the current literature by: (1) including older adults, (2) investigating insomnia as a potential risk factor for chronic pain, (3) evaluating the role of endotoxin-induced affective disturbances on pain sensitivity, and (4) assessing sex differences in endotoxin-induced hyperalgesia.
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1. Introduction

Chronic pain is a common condition among older adults (Alexopoulos, 2005; Patel et al., 2013), with incidence rates increasing as a function of age (Solhaug et al., 2012; Brattberg et al., 1997). Despite older adults (≥50 years old) being more likely to develop chronic pain, these individuals are often excluded from clinical trials evaluating the efficacy of new pharmacological treatments for pain conditions (Paeck

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et al., 2014). This is particularly concerning because older adults are most frequently prescribed analgesics for pain management (Paulose-Ram et al., 2003; Campbell et al., 2010) and are most at risk for experiencing negative consequences of analgesic medications (Field et al., 2004). As such, it may be beneficial to consider novel non-pharmacological treatments that could reduce pain symptoms in older adults.

One important and modifiable risk factor for chronic pain is insomnia, which is defined as difficulties in initiating or maintaining sleep, with accompanying daytime impairment (First, 2014). Insomnia is prevalent in both chronic pain populations (Smith et al., 2001; Morin et al., 2006) and among older adults (Ancoli-Israel and Cooke, 2005). Prior work has demonstrated that cognitive-behavioral treatments for insomnia improves sleep and may reduce pain symptoms in older adults (*e.g.,* Vitiello et al., 2009; McCurry et al., 2021). Reports also show that more restorative sleep associates with greater remission of pain symptoms in patients with chronic widespread pain (Davies et al., 2008). Interestingly, prospective cohort studies demonstrate that pain-free individuals with sleep disturbances are more likely to develop chronic pain at follow-up than those who sleep well (Gupta et al., 2007; Sanders et al., 2016). Taken together, this evidence suggests that insomnia frequently precedes and predicts the development of chronic pain (Finan et al., 2013), further validating the role of insomnia as an important modifiable risk factor for pain symptoms in older adults.

Evaluating the mechanisms by which insomnia and pain are linked could provide further evidence to understand the role of insomnia in the development of chronic pain conditions. Patients with chronic pain commonly present with central sensitization, which involves afferent firing of nociceptive neurons in the absence of ongoing tissue injury, and neuroplastic changes in regions of the brain and spinal cord that are involved in pain processing. Individual differences in central sensitization can be measured in the laboratory by assessing endogenous capacity to inhibit and facilitate pain (Basbaum, 1999; Bradley and McKendree-Smith, 2002; Melzack et al., 2001). Endogenous pain *inhibition* can be assessed by quantitative sensory tests of conditioned pain modulation, or the phenomena that the presence of one noxious stimulus can diminish pain intensity for a second, co-occurring noxious stimulus (Willer et al., 1989). Endogenous pain *facilitatory* processes can be assessed by temporal summation, which includes repeated presentations of identical noxious stimuli that leads to greater perceived pain (Willer et al., 1989). Individuals with chronic pain conditions show reduced pain inhibition (Lautenbacher and Rollman, 1997; Maixner et al., 1995; Finan et al., 2013; Peters et al., 1992; Pielsticker et al., 2005) and enhanced pain facilitation (Price et al., 2002; Staud et al., 2001; Maixner et al., 1998; Bragdon et al., 2002). Furthermore, endogenous pain inhibitory and facilitatory processes appear to contribute to both the development and maintenance of chronic pain disorders (Granovsky, 2013; Edwards, 2005; Wilder-Smith et al., 2010; Petersen et al., 2015).

In addition to central sensitization, a second aspect of pain processing that could be impacted by insomnia is affective pain modulation. Affective pain modulation refers to the phenomena that positive emotions reduce pain, while negative emotions enhance pain, which can be assessed in the laboratory by manipulating mood while simultaneously delivering noxious stimuli (Meagher et al., 2001). For example, a wealth of research has demonstrated that music can reduce both acute and chronic pain in medical settings, presumably due to music-induced increases in positive affect (Lee, 2016; Lunde et al., 2019). Along these lines, experimental studies are conducted using both acoustic and visual stimuli to evoke positive and negative emotional states while receiving noxious stimuli. To date, findings remain mixed on whether various pain conditions show impairments in affective pain modulation. For instance, patients with rheumatoid arthritis, recurrent back pain, and migraine demonstrated affective pain modulation comparable to pain-free controls (Arnold et al., 2008; de Tommaso et al., 2009; McPhee and Graven-Nielsen, 2022). By contrast, patients with fibromyalgia fail to downregulate their pain during positively valence stimuli, despite reporting similar emotional responses to the experimental stimuli as the pain-free participants (Rhudy et al., 2013; Kamping et al., 2013; but also see Arnold et al., 2008). While still preliminary, it is feasible that some widespread chronic pain conditions, such as fibromyalgia, may impact the ability of affect to modulate pain. Taken together, central sensitization and affective pain modulation could provide potential mechanisms by which insomnia can enhance risk for chronic pain conditions.

Along these lines, insomnia has been shown to impair both central sensitization and affective pain modulation. For example, insomnia and experimental sleep disruption both reduce conditioned pain modulation (*i.e.,* inhibitory capacity; Haack et al., 2012; Smith et al., 2007; Edwards et al., 2009), with findings potentially more pronounced in women than men (*e.g.,* Eichhorn et al., 2018). Similarly, sleep disruption and greater insomnia symptom severity associates with more impaired conditioned pain modulation in patients with chronic pain (Edwards et al., 2009; Paul-Savoie et al., 2012; ME Petrov et al., 2015; Lee et al., 2013; Campbell et al., 2015). By contrast, data on temporal summation (*i.e.,* facilitatory capacity) are more mixed, with some studies finding that insomnia or sleep disturbances enhance pain facilitation (e.g., M. E. Petrov et al., 2015; Edwards et al., 2011), while other studies report null findings (Haack et al., 2012; Schuh-Hofer et al., 2013). To date, three studies have investigated the relationship between sleep and affective pain modulation, all of which suggest that poorer sleep may blunt affective pain modulation (Finan et al., 2017; DelVentura et al., 2014; Huber et al., 2022). Therefore, insomnia appears to impact central sensitization and affective pain modulation in ways that could plausibly increase risk for pain chronification in susceptible individuals.

While it is plausible that insomnia increases risk for chronic pain via central sensitization and/or affective pain modulation, the underlying mechanisms remain unknown. Two potential mechanisms of interest are inflammation and affective disturbance. A recent meta-analysis that investigated the relationship between sleep disturbances and inflammation found that both sleep disturbances and long sleep duration (>8 hours) increased interleukin-6 (IL-6), but not tumor necrosis factor -alpha (TNF- α; Irwin et al., 2016). Experimental studies also suggest that partial and full sleep deprivation can activate intracellular signaling pathways involved in inflammation and upregulation of IL-6 and TNF-α RNA transcription (Irwin et al., 2006, 2008). While fewer studies have examined the relationship between sleep disturbances and interleukin-1β (IL-1β), initial evidence suggests that experimental total sleep deprivation (40hrs; Frey et al., 2007) and poor sleep quality (Milrad et al., 2017; Prather et al., 2009) are associated with greater levels of circulating IL-1β. Furthermore, improvements in sleep quality also correlates with lower levels of circulating IL-1β (Ng et al., 2022). Taken together, these data suggest that insomnia and behavioral sleep disturbances could exacerbate pain and potentially lead to pain chronification in susceptible individuals by increasing inflammatory cytokines such as IL-6, TNF- α, and IL-1β.

Animal models provide substantial evidence for the role of IL-6, TNF- α, and IL-1β in central sensitization. Levels of TNF- α, IL-6, and IL-1β are all increased following peripheral nerve injury and are temporally aligned with the onset and maintenance of hyperalgesia and/or allodynia (reviewed in Marchand et al., 2005). Furthermore, administration of IL-6, IL-1β, and TNF- α antagonists can reduce the magnitude of allodynia, hyperalgesia, and pain behaviors following nerve damage (Sommer et al., 2001a; Sommer et al., 2001b; Lindenlaub et al., 2000; Schafers et al., 2001; Sommer et al., 1999). Similarly, IL-6 knockout mice demonstrate less hyperalgesia following nerve damage than their wildtype littermates (Ramer et al., 1998; Murphy et al., 1999). It has also been demonstrated that greater concentrations of TNF- α, IL-6, and IL-1β can lead to hyperexcitability of nociceptive cells in the dorsal horn by facilitating glutamatergic signaling (TNF- α), reducing GABA-ergic signaling (IL-6), or both (IL-1β; Kawasaki et al., 2008). In sum, IL-6, TNF- α, and IL-1β are notable inflammatory markers by which insomnia could increase central sensitization. It is also noteworthy that

no prior research has examined the role of inflammation in affective pain modulation, highlighting an important gap in the field.

In addition to inflammation, affective disturbance (*i.e.,* increased negative affect and decreased positive affect) is another mechanism that could explain the relationship between insomnia and altered pain processes. Ecological momentary assessments of sleep and affect demonstrate that poorer sleep associates with lower positive affect and, to a lesser extent, increases in negative affect in both healthy sleepers (Bower et al., 2010; Kalmbach et al., 2014; de Wild-Hartmann et al., 2013; but also see Wong et al., 2021) and individuals with insomnia (Buysse et al., 2007). Furthermore, experimental studies that disrupted sleep continuity by forced nighttime awakenings also reduce positive affect and enhance negative affect (Finan et al., 2015; Finan et al., 2017; Reid et al., 2023). Importantly, the relationship between sleep and affect is believed to be bidirectional (Kahn et al., 2013), potentially suggesting that impairments in one could lead to a negative feedback loop that further exacerbates symptoms.

Prior work demonstrates that affective disturbance can impact both central sensitization and affective pain modulation. When measured in the laboratory, higher state positive affect was correlated with reduced pain facilitation (*i.e.,* temporal summation). Similarly, depressive symptoms – which are often characterized by both high negative affect and low positive affect – are associated with a blunted ability to inhibit heat pain (*i.e.,* conditioned pain modulation; Nahman-Averbuch et al., 2016). Interestingly, negative affect was uncorrelated with pain facilitatory capacity (Finan et al., 2013). In a similar vein, depression also impairs affective pain modulation, such that patients with depressive symptoms report similar pain intensities during positive, negative, and neutral mood manipulations (Terry et al., 2013). As such, affective disturbance may impact pain by altering both central sensitization and affective pain modulation.

In sum, the current study aims to understand how insomnia, inflammation, and affective disturbances may interact to impact indices of central sensitization and affective pain modulation in older adults (Fig. 1). The study includes 121 participants (44.6% female; ages 50–76) both with and without insomnia who were recruited as part of the parent project, Sleep and Healthy Aging Research on Depression (SHARE-D). All interested participants were screened for eligibility and separately consented for the current study – Healthy Aging Research on Pain (SHARE-P). Eligible participants attended an orientation session where they became familiar with the equipment and procedures used during the quantitative sensory testing. During the experimental session, participants were randomized to receive an injection of either saline or endotoxin (0.8g/kg), with both participants and experimenters blinded to injection condition. At this dose, endotoxin increases sensitivity to noxious stimuli starting at 1.5 hours until approximately 6 hours post-administration (Wegner et al., 2014). Endotoxin was used to experimentally enhance systemic inflammation and produce secondary disruptions in affect (*e.g.,* Eisenberger et al., 2009). Positive and negative affect were assessed hourly. Blood samples were collected every 30min for the first 2 h and then every hour for the remainder of the visit to measure changes circulating inflammatory markers IL-6, IL-1β, and TNF-α. Approximately 5.5 hours following the injection, participants completed a quantitative sensory testing battery, which assesses pain sensitivity, central sensitization, conditioned pain modulation, and affective pain modulation. In addition to the laboratory assessments, participants also completed ambulatory monitoring of pain, affect, depressive symptoms, and sleep at baseline, 3 months, 6 months, 9 months, and 12 months. Longitudinal assessments were performed to understand how endotoxin-induced changes in inflammation and affective disturbance interact with insomnia to predict future pain and depressive symptoms. Primary and secondary aims are noted below:

1.1. Primary aims

1. To evaluate differences in indices of central sensitization as a function of insomnia and experimental endotoxin exposure (0.8 ng/kg).
2. To evaluate differences in affective pain modulation as a function of insomnia and experimental endotoxin exposure (0.8 ng/kg).
3. To determine the extent to which endotoxin-induced affective disturbance accounts for alterations in central sensitization and affective pain modulation.
4. To determine whether individual differences in the endotoxin-induced inflammatory response are associated with changes in central sensitization and affective pain modulation and if they differ as a function of insomnia status.
5. To determine the extent to which (1) endotoxin-induced changes in inflammation, (2) affective disturbance in response to endotoxin, (2) central sensitization, and/or (4) affective pain modulation predict

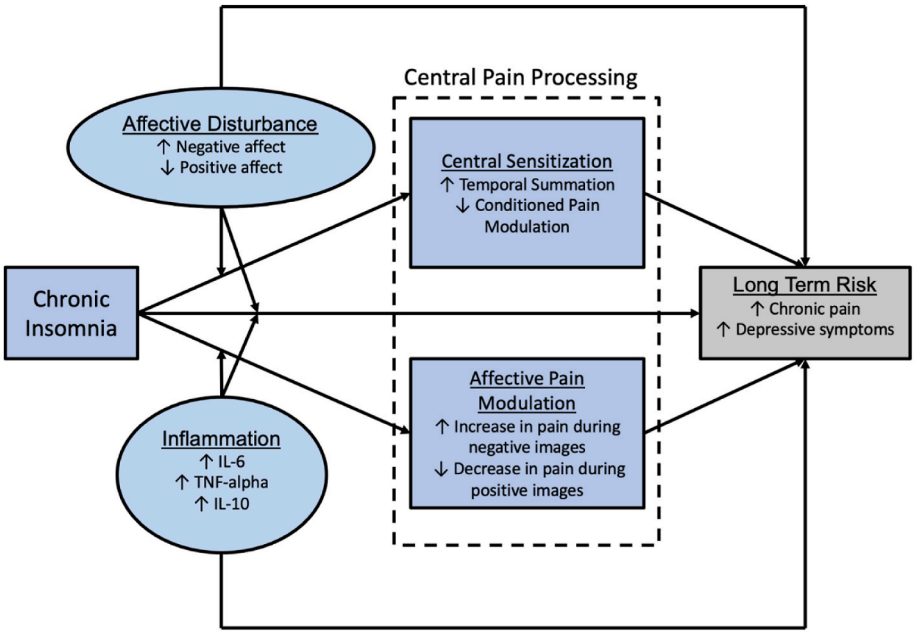

Fig. 1. Conceptual model of chronic pain risk.

self-reported pain and depressive symptoms over 1 year and whether these findings differ as a function of insomnia status.

1.2. Secondary aims

1. To understand how insomnia and endotoxin exposure impact additional aspects of pain, including (1) thermal conditioned pain modulation, (2) pressure pain threshold, (3) heat pain threshold, (3) heat pain tolerance, and (5) cold pain tolerance.
2. To assess whether inflammatory reactivity to endotoxin predicts the extent to which nightly changes in total sleep time are linked to next day increases in pain at follow-up (3, 6, 19, and 12 months).

2. Methods

2.1. Ethics approval

This study was approved by the University of California – Los Angeles (UCLA) Institutional Review Board under the parent study protocol (UCLA IRB # 16–000583) and was registered on clinicaltrials.gov (NIH R01AG057750-01).

2.2. Study design

The study follows a double-blinded, randomized, experimental design in which participants received an injection of either saline or 0.8ng/kg of endotoxin. Randomization to endotoxin or placebo conditions was completed by RO (study biostatistician) who did not interact with study participants. More information about randomization is detailed in the parent study protocol (Irwin et al., 2023). Approximately one third of the sample were predicted to meet criteria for insomnia disorder using the Structured Clinical Interview for DSM-5 (First et al., 2014), with the remaining participants having no current insomnia disorder.

The study included two laboratory visits and a longitudinal component that was delivered remotely. The first laboratory visit included a screening visit to gain consent, establish eligibility, orient participants to the pain assessments, and establish individual pain thresholds that were used in a later visit. During the second visit, participants received either a placebo or endotoxin injection and were monitored for 12 hours. Mood questionnaires and venous blood draws were completed throughout the visit in addition to pain testing that occurred approximately 5.5 hours post injection. The longitudinal component consists of two-week periods of data collection, during which, participants wore an actigraphy watch and completed smartphone diaries questions that assessed mood, pain, and sleep. Longitudinal assessments occurred at baseline and 3, 6, 9, and 12 months following the laboratory endotoxin challenge visit.

2.3. Participant recruitment

Participants were recruited through Genesys Sampling Systems (Fort Washington, PA) and the UCLA Clinical and Translational Science Institute (CTSI) Informatics Program. Households within 15 miles of the University of California – Los Angeles Westwood Campus that included at least one person over 60 years old were sent brochures and letters that detailed the parent study and provided study contact information. Staff also called participants to confirm that they received the brochures and to assess interest. In June 2020, an IRB modification was approved to expand the range of study participants to include individuals 50–80 years old. Since June 2020, brochures and letters were sent to households with at least one person over the age of 50 years old. Participants were originally compensated $2,405 for completing all study procedures. The compensation was reduced to $1,500 in February 2020 to reduce costs during the pandemic. Participants who did not complete the entire study received prorated compensation based on the number of study visits completed.

2.4. Eligibility criteria

Participants were required to be enrolled in the UCLA SHARE-D study (Irwin et al., 2023) to be considered for the current study (SHARE-P). Participants were excluded if: they scored ≥ 2 on the Graded Chronic Pain Scale (Von Korff et al., 1992); had a chronic pain disorder diagnosis (except for osteoarthritis, which is prevalent in older adults and its exclusion would reduce generalizability of findings); or had Raynaud's Syndrome (as symptoms could be exacerbated by the cold pressor test). Of note, the age criterion for eligibility was originally defined as 60 years or older; however, this was modified during the COVID-19 pandemic. As older adults were a high-risk group for infection and complications from COVID-19, participants 50–59 years old were able to participate in the study starting in June 2020 to resume data collection during the pandemic.

2.5. Overview of study procedures

The current study added to the study procedures detailed in SHARE-D (Irwin et al., 2023) in four ways: (1) adding pain assessments to the parent study's baseline visit, (2) including an orientation session for quantitative sensory testing, (3) adding quantitative sensory testing starting ~5hrs post endotoxin/saline injection, and (4) including longitudinal assessments of sleep, pain, and depressive symptoms at baseline, 3, 6, 9, and 12 months following the experimental portion of the study. The specific modifications are detailed below, organized by study visit.

2.6. Baseline Eligibility Assessment

Additional surveys were included in the parent project to determine eligibility and to provide a more detailed assessment of past and current pain symptoms:

Pain History Form. The pain history form was used to identify anatomic locations affected by past episodes of pain, pain history, and duration of chronic pain, including idiopathic disorders, such as irritable bowel syndrome.

The Brief Pain Inventory. The Brief Pain Inventory was included because of its sensitivity to changes in chronic pain symptoms in treatment studies (*e.g.,* Roth et al., 2000). The Brief Pain Inventory consisted of 11 items measuring pain severity and interference (Cleeland and Ryan, 1994).

Graded Chronic Pain Scale. The Grade Chronic Pain Scale has been well-validated and widely used in older samples (Smith et al., 1997; Elliott et al., 1999; Scherer et al., 2016). The Graded Chronic Pain Scale included seven items that measure chronic pain severity and pain related disability over a six-month period (Von Korff et al., 1992). Scores were classified into five severity/disability categories. Participants who receive a classification of < 2 were included in the study, as this score reflects non-specific, non-debilitating, and low severity pain (Scherer et al., 2016).

2.7. Orientation session

Overview. Participants who agreed to participate in the SHARE-P substudy signed the corresponding consent form and completed a brief (30–40min) orientation session to introduce quantitative sensory testing. The purpose of the session was to familiarize participants with equipment, pain rating scales, safety features, and study procedures. Participants were also informed that they could stop the assessment at any time without penalty. After arriving to the laboratory, participants were introduced to the pain rating scale on which they would be rating pain intensity on a 0 to 100 Vierck scale (0 = no sensation; 10 = discomfort; 20 = barely painful; 100 = intolerable; Vierck et al., 1997). Participants completed the following tasks in the order listed below.

Cold Pressor. Participants were instructed to place their dominant

hand into the cold water bath (2 °C) up to their wrist. They were asked to not make a fist and to ensure that their hands did not touch the bottom or sides of the machine. After 15 seconds of submersion, participants removed their hand from the cold water bath (VersaCool 7, Thermo Scientific) and provided a pain intensity rating (0–100).

Heat Pain Threshold. All heat stimuli were delivered by the Thermal Sensory Analyzer (Medoc, Medoc Pathway, Ramat Yishai, Israel), an FDA-approved peltier-based stimulator with a $3cm^2$ probe and built-in safety features to prevent tissue damage. The thermode was placed on the medial ventral dominant forearm, at least 1 inch above the wrist. The thermode was programmed to increase temperature from 31 °C at a rate of 0.5 °C per second until the participant first felt pain. When the participant first felt pain, they turned off the heat source by clicking a mouse with their non-dominant hand. Participants were then asked to rate the pain intensity. If participants rated pain intensity as either below 10 (discomfort) or above 30 (very weak pain), then they were provided with additional instructions to ensure task comprehension. The procedure was repeated for a total of two trials. The thermode was moved proximally on the ventral medial forearm between trials to avoid overlap.

Heat Pain Tolerance. The thermode was applied to the medial, ventral dominant forearm. Participants were instructed to turn off the thermode by clicking the computer mouse when the pain became intolerable. Participants were then asked to report the pain intensity of the stimulus. If the pain rating was under 30, then the 0–100 Vierk scale was reviewed with the participant. Only a single trial was conducted for heat pain tolerance at the orientation session, regardless of pain rating.

Pressure Pain Threshold. Noxious mechanical pressure stimuli were delivered by an electric algometer (Wagner Force Ten FDX, Wagner Instruments, Greenwich, CT) with a $1cm^2$ hard rubber probe, consistent with standard procedures (Brennum et al., 1989; Jensen et al., 1992). The algometer was placed on the middle of the upper trapezius muscle, posterior to the clavicle. Pressure increased at a rate of 1N/sec until participants reported that they first felt pain, which ended the procedure. Two pressure pain thresholds were acquired (right and left trapezius).

Mechanical Temporal Summation. A weighted punctate probe (number 7: 512 mN; PinPrick Stimulators, PP05 series, MRC Systems GmbH) with a flat contact area to prevent tissue damage was used to deliver mechanical noxious stimuli. The probe was placed on the dorsal middle phalange (third digit) of the non-dominant hand. First, the participant was given a single pinprick and asked to rate the pain intensity. Then, a series of 10 identical pinpricks were presented 1 s apart and the participant was asked to report the peak amount of pain they experienced during the series of 10 pinpricks. The participant was also asked to rate their pain 15 seconds after the series of 10 pinpricks.

Suprathrehold Heat Pain Ratings. A thermode was placed on the participant's non-dominant ventral, medial forearm approximately one inch from the wrist. There were three target temperatures that were presented in a fixed order (45 °C, 40 °C, then 49 °C) that were maintained for 3 s with an inter-stimulus interval of 10 seconds. The thermode was moved to a new position on the forearm in between each stimulus. Participants were asked to rate the pain intensity after each target temperature. If the pain intensity ratings were inconsistent with the heat stimuli (*i.e.,* rating 49 °C as less painful than 45 °C), then the participant received additional instructions. A total of three trials were performed.

Affective Pain Modulation – Image Presentation. Participants were presented a series of 12 images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999). The images were chosen to include high arousal positive (*i.e.,* erotica), negative (*i.e.,* mutilation), or neutral (*i.e.,* familiar objects) affective states. Consistent with prior work (Rhudy et al., 2005, 2008; Finan et al., 2017), the following IAPS images were used: Positive: 4668; 4653; 4608, 4677; Negative: 3060, 3168, 9405, 3030; Neutral: 7000, 7004, 7010, 7150. Participants rated their reactions to the images using two scales of the Self-Assessment Manikin (SAM; Bradley and Lang, 1994): one to measure image valence from 1 (negative) to 9 (positive) and a second to measure image arousal from 1 (calm) to 9 (excited).

Conditioned Pain Modulation – Pressure. Prior to starting the conditioned pain modulation task, a new pressure pain threshold was established, as detailed above. Then, participants placed their non-dominant hand in a cold-water bath (2 °C), as previously instructed (see *Cold Pressor* section above). After 20 seconds, the participants rated the cold pain intensity. Then, a pressure pain threshold was established on the contralateral trapezius muscle while their hand remained in the cold-water bath. After the pressure pain threshold was recorded, participants removed their hand from the water bath and provided a maximum cold pain rating. Pain ratings were taken again at 30 and 60 seconds after withdrawing their hand from the cold water bath.

Conditioned Pain Modulation – Thermal. A thermode was placed on the participants' dominant ventral, medial forearm. The participant submerged their contralateral (non-dominant) hand in the cold-water bath (2 °C). After 20 seconds the participant rated the cold pain intensity. Then, the thermode elicited a 3sec thermal stimulus at the highest temperature that was tolerated during the suprathrehold heat pain task (40 °C, 45 °C, or 49 °C; described above). Pain intensity ratings were collected after the thermal pain stimulus, then the participant removed their hand from the cold water bath. Pain intensity ratings were taken again at 30 and 60 seconds after withdrawing their hand from the cold water bath.

2.8. Experimental session

A quantitative sensory testing battery was added to the parent project's experimental study visit (see Fig. 2; Irwin et al., 2023). Briefly, participants reported to the laboratory at approximately 8am. At this time, a nurse blinded to condition (endotoxin vs saline) measured their height, weight, and vital signs. Participants did not complete the study visit if (a) blood pressure $>$ 160/120 or $<$ 90/60, (b) pulse $<$ 50 bpm, or (c) temperature $>$ 99.5F. A venous catheter was inserted on both forearms. Blood sampling was completed using the dominant forearm, while the non-dominant forearm received a continuous saline flush (150 cc/hr) for endotoxin or placebo administration. Baseline blood samples and questionnaire data were then completed. After baseline assessments (~90min) participants were either injected with saline or 0.8ng/kg of endotoxin (*E. coli* O:113; provided by the National Institutes of Health). Participants completed hourly surveys to assess mood (self-reported Profile of Mood States; POMS; McNair, Lorr, & Droppleman, 1992). Blood samples were collected every 30min for the first 2 h and then every hour until 12 hours post-injection to assess inflammatory cytokines, including IL-6, TNF, IL-8, and IL-10; Irwin et al. (2023). Quantitative sensory testing was initiated ~5.5 hours post-injection, with the entire procedures lasting 60–90min. Blood pressure and heart rate were assessed (SmartLinx Vitals Plus, Capsule Technologies) prior to starting the quantitative sensory testing and again before the conditioned pain modulation tasks. The quantitative sensory testing battery included the following assessments, in the order listed: Heat pain threshold, heat pain tolerance, pressure pain threshold (randomized order for thermal and pressure stimuli); affective pain modulation, mechanical temporal summation, conditioned pain modulation (trial 1: pressure; trials 2–3: thermal), and cold pressor pain tolerance (Table 1).

McGill Pain Questionnaire – Short Form. The McGill Pain Questionnaire – Short Form is a 15-item survey used to capture different sensory and affective adjectives to describe current painful sensations from 0 (none) to 3 (severe; Melzack, 1987; Melzack and Raja, 2005). Participants completed this form hourly during the experimental session to assess changes in pain throughout the procedure. This measure has good test re-retest reliability assessed within the same day (Yakut et al., 2007), has been previously used to assess hourly changes in pain experiences (Hosomi et al., 2013), and is sensitive to same-day treatment responses (Rubinstein et al., 2014).

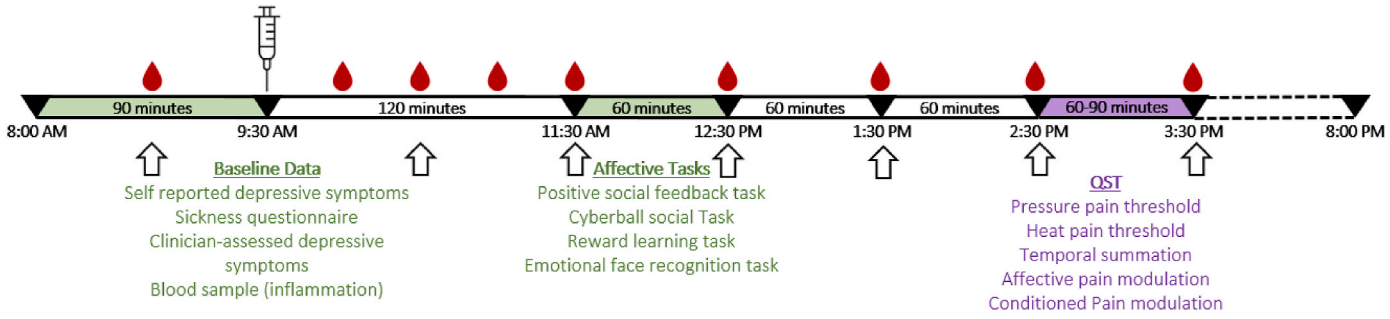

Fig. 2. Integration of the Parent Project (SHARE-D) and Current Project (SHARE-P) during the Experimental Visit. Note. This figure illustrates of how the SHARE-P protocol fits within the parent project. The parent project is represented in green, while SHARE-P is in purple. The red droplets represent timing for blood draws, whereas the arrows indicate when mood and pain surveys were administered.\. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Thermal (Heat) Pain Threshold. The thermode (Medoc, Medoc Pathway, Ramat Yishai, Israel) was placed on the medial, ventral dominant forearm, one inch from the wrist. The thermode gradually increased its temperature until the participant reported that they first felt pain. Participants were also asked to rate the pain intensity. The procedure was repeated after moving the thermode to a new location on the forearm, for a total of two trials.

Thermal (Heat) Pain Tolerance. The thermode was again placed on the medial, ventral dominant forearm. The thermode gradually increased its temperature until the participant reported that the pain was intolerable. Participants also rated the pain intensity. The thermode was removed to a new location before repeating the procedure for a second trial.

Pressure Pain Threshold. An electric algometer (Wagner Force Ten FDX, Wagner Instruments, Greenwich, CT) was used deliver pressure to the each of the following locations: middle of the upper trapezius muscle, masseter, and middle insertion point of the quadriceps. All assessments were made at the middle of the muscle belly. Pressure increased at a rate of 1N/sec until participants reported that they first felt pain, which ended the procedure. Pressure pain thresholds were established twice on the right and twice on the left, resulting in four trials per location.

Affective Pain Modulation. The task included three blocks in a randomized order, with each block corresponding to a particular valence (*i.e.,* positive, negative, and neutral). Each block included four trials. During each trial, participants viewed an image while receiving a thermal stimulus (46 °C or 48 °C) on their dominant ventral, medial forearm. Participants then rated the valence and arousal of each image and pain intensity of the thermal stimulus. Each block consisted of two 46 °C and two 48 °C stimuli presented in a randomized order. Participants had a 1 min break between blocks. The thermode was repositioned by one inch along the forearm between blocks. Images were identical to those presented during the orientation session.

Mechanical Temporal Summation. A weighted punctate probe (number 3: 32 mN; PinPrick Stimulators, PP05 series, MRC Systems GmbH) was placed on the dorsal middle phalange (third digit) of the non-dominant hand. Participants rated their pain to a single pinprick. Then, a series of 10 pinpricks was presented 1 second apart. Participants rated their peak pain in response to the series of 10 pinpricks, and again 15 seconds after the series of pinpricks. The procedure was repeated using the following probes: number 5 (128 mN), number 6 (256 mN), and number 7 (512 mN).

Conditioned Pain Modulation – Pressure. First, a pressure pain threshold was established on the trapezius muscle contralateral to the non-dominant hand. Participants then placed their non-dominant hand in a cold-water bath (2 °C) for 20 seconds. At that time, participants reported a cold water pain rating. Then, another pressure pain threshold was established on the contralateral trapezius muscle while their hand remained submerged in the cold water bath. Participants rated their maximal cold water pain and provided additional pain ratings 30 and 60 seconds after withdrawing their hand from the water bath. If participants could not keep their hand submerged for 20 seconds, then they were asked to rate their cold pain upon withdrawing their hand from the water bath and completed the pressure pain threshold immediately thereafter.

Conditioned Pain Modulation – Thermal. Two trials were completed for the thermal conditioned pain modulation. For the first trial, the highest tolerated heat pain temperature established at the orientation session was used during the task (40 °C, 45 °C, or 49 °C). Prior to the second trial, a new heat pain threshold was established by administering three target temperatures that in a standardized order (45 °C, 40 °C, then 49 °C) with an inter-stimulus interval of 10 seconds. The highest tolerated temperature was used in the second trial of thermal conditioned pain modulation. During both trials, a thermode was placed on the dominant ventral, medial forearm. The participant submerged their non-dominant hand into the cold water bath (2 °C) for 20sec. At 20 seconds, participants rated the cold pain intensity. Then, the thermode presented a 3 s stimulus (40 °C, 45 °C, or 49 °C). Heat pain intensity ratings were collected immediately after the thermal stimulus. Cold pain ratings were taken again at 30 and 60 seconds after withdrawing their hand from the cold water bath.

Cold Pressor. Participants were instructed to keep their non-dominant hand in the cold-water bath (2 °C) as long as possible, until the pain is no longer tolerable. Participants reported when they first felt pain (*i.e.,* cold pain threshold). The time at which participants removed their hand from the cold-water bath was also recorded (*i.e.,* cold pain tolerance). Pain intensity ratings were taken every 20sec while the participants hand was submerged in water, with an undisclosed maximum time limit of 5 min. After withdrawing their hand from the cold water bath, participants reported the maximum cold pain intensity and pain intensity at 30 and 60 seconds post-withdrawal.

2.9. Longitudinal ambulatory data collection

Longitudinal data were collected remotely at baseline, 3mo, 6mo, 9mo, and 12mo post-experimental session via REDcap (Research Electronic Data Capture; Harris et al., 2009; Harris et al., 2019). Participants accessed REDCap by their personal smartphone or tablet.

Graded Chronic Pain Scale. The graded chronic pain scale (three months version; Von Korff et al., 1992) was collected at each timepoint. The scale is described above under 'Baseline Eligibility Assessment.'

Patient Health Questionnaire – 9 items. The Patient Health Questionnaire as administered at each time point to assess depressive symptoms (Kroenke et al., 2001).

Smartphone Diaries. Surveys were administered in the morning and evening daily for 14 consecutive days via REDcap (Harris et al., 2009, 2019). Participants without a smartphone received a study tablet with a data plan to complete daily diary surveys. Morning surveys consisted of a sleep diary (detailed in parent study protocol; Irwin et al., 2023), while

Table 1
Overview of quantitative sensory testing by study session.

Orientation Session		Experimental Session	
Order	Task	Order	Task
1	*Heat Pain Threshold* Medial ventral dominant forearm 2 trials	1 or 2*	*Heat Pain Threshold* Medial ventral dominant forearm 2 trials
2	*Heat Pain Tolerance* Medial ventral dominant forearm 1 trial	2 or 3*	*Heat Pain Tolerance* Medial ventral dominant forearm 2 trials
3	*Pressure Pain Threshold* Trapezius muscle (right and left) 2 trials; 1 trial per side of body	1 or 2*	*Pressure Pain Threshold* R/L trapezius, R/L masseter, R/L quadriceps 4 trials/site (2 trials on each side)
4	*Mechanical Temporal Summation* Middle finger of non-dominant hand Probe: # 7 1 trial	4	*Affective Pain Modulation* Medial ventral dominant forearm; 46 and 48 °C View 12 images † Ratings for valence and arousal (images) & pain
5	*Suprathreshold Heat Pain Ratings* Medial ventral non-dominant forearm Temperatures: 40, 45, and 49 °C 3 trials	5	*Mechanical Temporal Summation* Middle finger of non-dominant hand Probes: #3, #5, #6, #7 1 trial
6	*Affective Pain Modulation* No noxious stimuli; view 12 images Ratings for valence and arousal (images)	6	*Conditioned Pain Modulation – Pressure* Non-dominant hand in 2 °C water bath Pressure: contralateral trapezius Established new pressure threshold before task 1 trial
7	*Conditioned Pain Modulation – Pressure* Non-dominant hand in 2 °C water bath Pressure: contralateral trapezius Established new baseline pressure threshold 1 trial	7	*Conditioned Pain Modulation – Heat* Non-dominant hand in 2 °C water bath Heat: contralateral ventral medial forearm Trial 1: highest tolerated (orientation; step 5) Trial 2: established new temp (40, 45, or 49 °C)
8	*Conditioned Pain Modulation – Heat* Non-dominant hand in 2 °C water bath Heat: contralateral ventral medial forearm Used highest tolerated temp from step 5 1 trial	8	*Cold Pressor Tolerance* Non-dominant hand in 2 °C water bath 1 trial; 5 min maximum

Note. *Heat and pressure pain tasks were completed in a randomized order between participants; † The same 12 images were presented during orientation and experimental sessions. Experimental session included 3 blocks (positive, negative, neutral) with each block containing 4 images. Block order was randomized across study participants.

evening surveys include questions on pain, caffeine and alcohol intake, medication use, and positive and negative affect. Automated text message reminders were sent when participants did not complete the scheduled assessments.

Daily Diary – Pain Intensity. The Pain Intensity Index was used to assess daily and two-week average pain intensity (Huskisson, 1983; Jensen and McFarland, 1993). Participants were asked to rate their lowest pain, highest pain, and average pain across the day on a 0 (barely noticeable) to 10 (worst pain imaginable) scale. Daily pain was assessed by averaging the three pain ratings across each day. The two-week average pain was calculated by averaging across all pain ratings reported during the two-week period of daily diaries entries.

Daily Diary – Positive and Negative Affect. Positive and negative affect were assessed by rating the extent to which participants felt three positive emotions (happy, calm, and agreeable) and three negative emotions (sad, anxious, and annoyed) during the day on a 0 (not at all) to 100 (extremely) scale. These emotion words were selected because they appear on both the Profile of Mood States (McNair et al., 1992) and Positive and Negative Affect Schedule – X (Watson and Clark, 1994) scales. The items within each valence were averaged to create daily indices of positive and negative affect. Our prior work in a sample of older adults demonstrated that emotion words assessed in this way were highly correlated within the same valence ($r = .72$ to 0.80) and showed excellent internal consistence (Chronbach's $\alpha \geq 0.85$; Finan Quartana, & Smith, 2013).

Wrist Actigraphy. Participants received triaxial accelerometers to wear on their non-dominant wrist for 14 days to provide behavioral assessments of sleep. Wrist actigraphy was used to estimate total sleep time according to a standard protocol (Ancoli-Israel et al., 2015). Two models were used to collect wrist actigraphy data: Octagonal MotionLogger with a light sensor (Ambulatory Monitoring, Inc; Ardsley, NY, USA) and ActiWatch wGT3X-BT (Actigraph LLC; Pensacola, FL, USA). Data were autoscored using the validated Cole-Kripke algorithm (Cole et al., 1992) within either minimotion logger or actilife software. Actigraphy patterns were then systematically examined for validity and extreme sleep period deviations from the diary data. Changes were made to the autoscored major sleep period(s) times based on a standardized procedures developed by our lab:

1) If there is a ≤ 60 minute deviation between the auto-scored sleep and the diary "lights out" time or the diary "time out of bed upon final waking" time, we defer to the auto-scored sleep parameters.
2) If there is a > 60 minute deviation between the auto-scored sleep at "lights out" or "time out of bed upon final waking time" and the diary, the actigraphy record is edited to match the sleep diary times if the activity patterns demonstrate congruence with the sleep diary data. Congruence for Lights out is demonstrated by a clear observable decrease in activity counts. Congruence for time out of bed upon final waking time is demonstrated by a clear observable increase in activity counts. If there is not clear congruence between activity patters and the diary, then the autoscored sleep period markers are used.
3) Whenever the auto-scoring breaks a night of sleep into two distinct sleep periods, actigraphy data should be rescored as one sleep period if consistent with diary data.

3. Outcomes

3.1. Primary outcomes

Mechanical Temporal Summation (Aims 1–3). Temporal summation will be assessed using the windup ratio, which is calculated by taking the peak pain intensity from a series of 10 pinpricks divided by the pain intensity from a single pinprick. The wind-up ratio will be Z-scored within each probe and then averaged across probes to create an aggregate temporal summation index (primary outcome). Change scores will also be used to calculate temporal summation by subtracting the peak pain rating during 10 successive pinpricks from the pain rating during a single pinprick. Change scores will also be Z-scored and averaged across probes (secondary outcome).

Conditioned Pain Modulation – cold water and pressure pain (Aims 1–3). Percent change in pressure pain threshold during the cold pressor task compared to the pressure pain threshold assessed just prior to cold water submersion.

Affective Pain Modulation (Aim 2–3). Affective pain modulation is assessed by comparing self-reported pain across the three conditions

(negative, positive, neutral).

Self-Reported Pain (Aim 4). Longitudinal assessment of the Pain Intensity Index using diary data and averaged across the two-week period at baseline and 3, 6, 9, and 12 months.

Depressive Symptoms (Aim 4). Longitudinal assessments of depressive symptoms using the Patient Health Questionnaire – 9 item at baseline and 3, 6, 9, and 12 months.

3.2. Secondary outcomes

Conditioned Pain Modulation – cold water and heat pain. Percent change in heat pain threshold during the cold pressor task compared to the heat pain threshold assessed just prior to cold water submersion. Raw difference scores will also be reported.

Pressure Pain Threshold. Pressure pain threshold was assessed at three sites: trapezius, masseter, and middle insertion of the quadriceps. Four trials were completed for each site (two on the left side; two on the right side). Values will be Z-scored for each site and averaged to create an index score.

Heat Pain Threshold. The temperature that first elicits pain, averaged across two trials.

Heat Pain Tolerance. The temperature at which the participant identifies the pain as intolerable, averaged across two trials.

Cold Pain Tolerance. The time it takes for the participant to withdraw their hand from the cold water bath.

Next Day Pain. Daily pain intensity ratings assessed by the Pain Intensity Index at baseline and 3, 6, 9, and 12 months.

4. Statistical methods

4.1. Sample size

A maximal sample size of $N = 148$ (placebo $N = 74$; endotoxin $N = 74$) has been pre-determined by the parent project. Assuming the target recruitment goal is reached, then the study will be 80% powered to detect a small-to-medium effect size for Aim 1 and Aim 2 ($d = .48$) and a moderate effect size for Aim 3 ($d = .80$) and Aim 4 ($d = .94$).

4.2. Statistical analysis

Group differences will be evaluated by ANOVA, t-tests, and/or chi-squares, depending on the number of comparisons and nature of the variables (dichotomous vs continuous). Time since injection will be included as a covariate in all models. Plots and descriptive statistics, and statistical tests of distribution (i.e. skewness and kurtosis analyses) will be used to determine if assumptions of proposed models are appropriate. Hypothesis tests will be two-sided with p-values $< .05$ considered statistically significant, unless otherwise indicated following correction for multiple comparisons.

Aim 1. To evaluate differences in indices of central sensitization as a function of insomnia and experimental endotoxin exposure (0.8 ng/kg).

It is hypothesized that individuals with insomnia will demonstrate greater central sensitization (enhanced temporal summation, less conditioned pain modulation) following endotoxin exposure relative to good sleepers. Separate 2 (healthy sleeper vs insomnia) x 2 (placebo vs endotoxin) ANCOVAs will be used to assess group differences in (1) temporal summation and (2) conditioned pain modulation.

Aim 2. To evaluate differences in affective pain modulation as a function of insomnia and experimental endotoxin exposure (0.8 ng/kg).

It is hypothesized that exposure to endotoxin and the presence of insomnia will associate with impaired affective pain modulation (*e.g.,* greater pain facilitation during unpleasant images and lower pain inhibition during pleasant images). A 2 (healthy sleeper vs insomnia) x 2 (placebo endotoxin) x 3 (positive vs negative vs neutral) between/within ANCOVA will be used to evaluate differences in pain ratings between affective valences as a function of endotoxin and insomnia. Planned pairwise comparisons (*i.e.,* positive vs neutral; negative vs neutral; positive vs negative) will be tested via interactions between sleep status and endotoxin/placebo assignment.

Aim 3. To determine the extent to which endotoxin-induced affective disturbance accounts for alterations in central sensitization and affective pain modulation.

Separate regression models will be used to investigate the extent to which any endotoxin-related increases in negative affect and decreases in positive affect moderate the effect of endotoxin exposure on temporal summation, conditioned pain modulation, and affective pain modulation.

Aim 4. To determine whether individual differences in the endotoxin-induced inflammatory response are associated with changes in central sensitization and affective pain modulation and if they differ as a function of insomnia status.

Inflammatory responses to endotoxin exposure will be quantified using an area under the curve approach (Pruessner et al., 2003). Inflammatory responses will be assessed for IL-6 (primary outcome), TNF-α and IL1β (secondary outcomes). Analyses will only include participants who received endotoxin during the experimental visit. Separate general linear models will be used to assess the main effect of inflammatory responses to endotoxin and its interaction with insomnia status on temporal summation, conditioned pain modulation, and affective pain modulation.

Aim 5. To determine the extent to which (1) endotoxin-induced changes in inflammation, (2) affective disturbance in response to endotoxin, (2) central sensitization, and/or (4) affective pain modulation predict self-reported pain and depressive symptoms over 1 year and whether these findings differ as a function of insomnia status.

Analyses will be restricted to participants who received endotoxin during the experimental session. Multiple regression analyses will be used to assess whether endotoxin-induced inflammatory reactivity (area under the curve) associates with pain intensity (grand mean of Pain Intensity Index at 3, 6, 9, and 12 months; primary outcome) and the frequency of moderate-to-severe pain days (secondary outcome). Moderate-to-severe pain days are defined as a rating of $\geq 30/100$ rating. Models will also investigate three-way interactions between inflammatory reactivity, insomnia status (dichotomous), and (1) temporal summation, (2) conditioned pain modulation, (3) affective pain modulation, (4) negative affect and (5) positive affect assessed during experimental visit. Similar analyses will be conducted using depressive symptoms and affect as outcomes variables, as measured by the PHQ-9 (primary) and diary POMS (secondary), respectively.

5. Discussion

The current study evaluates how insomnia, inflammation, and affective disturbances interact to alter pain processing in older adults. The current study has notable strengths that address various gaps in the literature. First, the study uses endotoxin as a model of pain, as it reliably increases pain sensitivity to thermal and deep pressure stimuli, with limited effects on mechanical pain sensitivity (Karshikoff et al., 2015; de Goeij et al., 2013). To date, relatively few studies have investigated endotoxin-induced hyperalgesia, with the majority of studies limited to young, male participants (Hutchinson et al., 2013; DellaGioia and Hannestad, 2010; Benson et al., 2012; Benson et al., 2015; Wegner et al., 2014; Wegner et al., 2015; de Goeij et al., 2013; Janum et al., 2016; but also see Karshikoff et al., 2015; Wegner et al., 2015). By including individuals with and without an insomnia diagnosis, the current study is also able to evaluate insomnia status as a potential risk factor for chronic pain. As such, the current study would extend prior work to understand whether endotoxin is a reliable model of pain in older (≥50 years old) men and women and whether insomnia further enhances endotoxin-induced hyperalgesia.

Another benefit of the current study is the thorough assessment of central sensitization (*i.e.,* pain inhibitory or facilitatory capacity) indices

of pain. Only a single study has assessed the effects of endotoxin on conditioned pain modulation, with the results suggesting that only women show impaired pain inhibition following endotoxin exposure (Karshikoff et al., 2015). Furthermore, no studies have yet demonstrated how endotoxin impacts pain facilitatory processes, as assessed by temporal summation. Thus, the current study will further explore how endotoxin impacts pain facilitatory and pain inhibitory processes in older men and women.

The current study also evaluates how affective disturbance (*i.e.,* increased negative affect and reduced positive affect) may impact the relationship between endotoxin administration and exaggerated pain sensitivity. The findings are currently mixed on whether endotoxin-induced increases in negative affect impact pain sensitivity (Benson et al., 2012; Wegner et al., 2014); however, pain assessments in these studies were limited to pain thresholds. By contrast, the current study directly assesses whether endotoxin can alter the ability of affect to regulate pain sensitivity using an affective pain modulation task.

In summary, the current study will further explore insomnia as a potential risk factor for pain using more precise measures of pain inhibitory and facilitatory processes in both male and female older adults. It will also investigate if inflammatory and pain responses to endotoxin predict risk of future pain or depression.

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Authors' contributions

MTS, MRI, CMC, and PHF conceived and designed the study. CMC was involved in ensuring fidelity of pain measures. NS and DC were involved in data collection and protocol implementation. The grant was awarded to MTS. CMD, KRH, MJR, and RO will conduct statistical analyses of primary outcome data. CMD drafted the manuscript, while all additional authors reviewed and approved the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Glossary

IL-1β: interleukin-1β
IL-6: interleukin-6
TNF- α:: tumor necrosis factor-alpha