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Enhanced facilitation and diminished inhibition characterizes the pronociceptive endogenous pain modulatory balance of persons living with HIV and chronic pain

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Abstract

Chronic pain in persons living with HIV (PLWH) may be related to alterations in endogenous pain modulatory processes (e.g., high facilitation and low inhibition of nociception) that promote exaggerated pain responses, known as hyperalgesia, and central nervous system (CNS) sensitization. This observational study examined differences in endogenous pain modulatory processes between 59 PLWH with chronic pain, 51 PLWH without chronic pain, and 50 controls without HIV or chronic pain. Quantitative sensory testing for temporal summation (TS) of mechanical and heat pain as well as conditioned pain modulation (CPM) were used to assess endogenous pain facilitatory and inhibitory processes, respectively. Associations among TS, CPM, and self-reported clinical pain severity were also examined in PLWH with chronic pain. Findings demonstrated significantly greater TS of mechanical and heat pain for PLWH with chronic pain compared to PLWH without chronic pain and controls. CPM effects were present in controls, but not in either PLWH with or without chronic pain. Among PLWH with chronic pain, greater TS of mechanical pain was significantly associated with greater average clinical pain severity. Results of this study suggest that enhanced facilitation and diminished inhibition characterizes the pronociceptive endogenous pain modulatory balance of persons living with HIV and chronic pain.

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Keywords

HIV; chronic pain; endogenous pain modulation; temporal summation; conditioned pain modulation

INTRODUCTION

Chronic pain is an important comorbidity that commonly affects persons living with HIV (PLWH). A recent review of the literature indicated that chronic pain may affect over half of all PLWH throughout their lifetimes, with increasing prevalence as these individuals age (Parker, Stein, et al., 2014). Peripheral neuropathy resulting from the neurotoxic effects of HIV itself as well as the medications used to treat HIV was widely considered the primary cause of chronic pain early in the antiretroviral treatment era (Dalakas, 2001; Gabbai, Castelo, et al., 2013). However, recent studies suggest a predominance of chronic musculoskeletal pain in PLWH that is non-neuropathic in nature (Jiao et al., 2016; Merlin, Cen, et al., 2012). It is common for chronic pain in PLWH to be widespread, affecting multiple body locations (Miaskowski et al., 2011). It is also becoming more widely appreciated that PLWH endure high-impact chronic pain that negatively impacts their ability to function and is associated with overall poor health outcomes. To illustrate, chronic pain in PLWH is associated with greater odds of functional impairment (Merlin et al., 2013), increased health care service utilization (Dobalian, Tsao, et al., 2004), suboptimal retention in HIV care (Merlin, Westfall, et al., 2012), and failure to achieve virologic suppression (Merlin et al., 2018). Despite mounting evidence attesting to the physical and mental health consequences of chronic pain in PLWH, very little is currently known about the neurophysiological processes that may relate to the development and perpetuation of chronic pain in this population.

The percept of pain is greatly influenced by the endogenous processing of ascending (i.e., incoming) nociceptive signals from peripheral afferents, which are powerfully modulated by complex descending inhibitory and facilitatory processes within the central nervous system (CNS) (Ossipov, Dussor, et al., 2010; Ossipov, Morimura, et al., 2014). The descending modulation of incoming nociceptive signals is manifested via pathways that originate at the level of the cerebral cortex, the thalamus, and the brainstem (Heinricher, Tavares, et al., 2009). Activation of these descending nociceptive modulatory processes often involves the release of inhibitory and/or excitatory neurotransmitters that can potently inhibit or facilitate the percept of pain, respectively (Staud, 2013). It has been suggested that the descending modulation of nociceptive signals within the CNS yields a pain inhibitory/facilitatory balance, which places individuals on a spectrum between antinociception and pronociception (Granovsky & Yarnitsky, 2013; Yarnitsky, Granot, et al., 2014). To illustrate, an individual expressing diminished inhibition and enhanced facilitation would be positioned on the pronociceptive side of the spectrum. As a result, this individual would express a more pain sensitive phenotype that increases the risk of developing (or worsening) a chronic pain condition. Conversely, an individual expressing efficient inhibition and non-enhanced facilitation would be positioned further on the antinociceptive side of the spectrum, and therefore express a less pain sensitive phenotype that would help prevent the

development of a chronic pain condition. The multiple, complex descending pathways involved in the modulation of nociceptive signals are referred to collectively as endogenous pain modulatory processes. The experience of chronic pain in PLWH may be related to alterations in endogenous pain modulatory processes (e.g., high facilitation and low inhibition of nociception) that promote hyperalgesia and CNS sensitization (Ossipov, 2012; Staud, 2012, 2013). Initial support for this possibility comes from research previously conducted by our group comparing responses to noxious heat and mechanical stimuli between PLWH without comorbid chronic pain and controls without HIV. Results revealed that PLWH demonstrated significantly exaggerated pain responses to the noxious heat and mechanical stimuli compared to controls (Goodin et al., 2017).

Experimental protocols designed to assess the endogenous inhibition or facilitation of pain are believed to better depict the clinical pain experience than the classical static parameters, such as pain thresholds (Yarnitsky et al., 2014). A commonly used protocol for the assessment of pain inhibition is conditioned pain modulation (CPM), which refers to the reduction in pain from one stimulus (the test stimulus) produced by the application of a second pain stimulus at a remote body site (the conditioning stimulus) (Nir & Yarnitsky, 2015). CPM is believed to reflect the perceptual manifestation of diffuse noxious inhibitory controls (DNIC) (Le Bars, 2002), whereby ascending projections from one noxious stimulus activate supraspinal structures that trigger descending inhibitory projections to the dorsal horn. The neurophysiological substrates that contribute to the CPM effect are thought to be opioidergic, serotonergic and noradrenergic in nature (Ossipov et al., 2010; Ossipov et al., 2014; Staud, 2013). Characterization of temporal summation (TS) responses provides information about pain facilitation resulting from enhanced nociceptive processing in healthy individuals and those with chronic pain (Magerl, Wilk, et al., 1998; Price, Hu, et al., 1977; Staud, Weyl, et al., 2014). TS refers to an increase in pain perception after application of a series of identical noxious stimuli delivered at sufficient frequency and intensity (usually 0.3Hz with fixed stimulus intensity). TS is presumed to be the psychophysical manifestation of wind-up (Staud, Vierck, et al., 2001). Wind-up is a phenomenon where repetitive stimulation of C primary afferents at rates greater than 0.3Hz produces a slowly increasing response of second-order neurons in the spinal cord (Magerl et al., 1998; Price et al., 1977), which is dependent on activation of the N-methyl-D-aspartate (NMDA) receptors (Eide, 2000).

Typically, individuals with various chronic pain conditions demonstrate pronociceptive phenotypes expressed either as enhanced TS (facilitation), less efficient CPM (inhibition), or both (Staud, 2012, 2013). The possibility of a pronociceptive phenotype in PLWH may be increased due to the direct effects of HIV itself on the CNS. HIV crosses the blood-brain barrier and damages neuronal tissue in the brain at least in part through NMDA receptor activation initiated by soluble neurotoxins from HIV-infected brain macrophages (O'Donnell et al., 2006; Spudich & Gonzalez-Scarano, 2012). NMDA-mediated neuronal damage due to HIV infection may then alter endogenous pain modulatory processes that facilitate nociception, resulting in the percept of greater pain severity. However, no study to date has investigated whether chronic pain in PLWH is related to the endogenous pain modulatory processes using experimental pain protocols such as TS and CPM. The aim of the present study was to characterize differences in endogenous pain modulatory processes among

PLWH with chronic pain, PLWH without chronic pain, and controls without HIV or chronic pain, as well as examine whether the endogenous pain modulatory processes represented by TS and CPM were associated with the clinical pain severity reported by PLWH with chronic pain. We hypothesized that: 1) PLWH with chronic pain would demonstrate greater TS and less CPM compared to PLWH without chronic pain and controls, and 2) greater self-reported clinical pain severity would be associated with greater TS and less CPM for PLWH with chronic pain. This study represents an important first step towards elucidating the endogenous pain modulatory profiles of PLWH with chronic pain, which may reveal targets for future research and intervention.

METHODS

Participants

A total of 110 PLWH were recruited from a large urban, HIV clinic in the southeast United States that provides comprehensive medical, behavioral, and social services to adults with HIV. Overall, this HIV clinic provides care to 3,457 PLWH, of which 76% are men, 23% are women, and 1% is transgender. Further, 64% identify as Black/African American, 31% as White/Caucasian, and 5% as Hispanic/Others. PLWH were separated into two groups according to their chronic pain status. We enrolled into this study 59 PLWH with chronic pain and 51 PLWH without chronic pain. Additionally, 50 individuals without HIV or chronic pain (controls) were also recruited from the local community via posted fliers and enrolled into the study. Each of these 160 total participants completed the study in its entirety. Study procedures were approved by our Institutional Review Board and carried out in accordance with guidelines for the ethical conduct of research. Written informed consent was obtained from each participant prior to the study and they were compensated a total of \$100 for their involvement.

Overview of Study Design

A flow diagram depicting matriculation through the study is presented in Figure 1. PLWH with and without chronic pain and controls who were interested in being part of this study were assessed for eligibility during an initial telephone screening. A review of medical records was also completed for PLWH with and without chronic pain. Eligible participants then presented to the laboratory to complete a single study session that lasted approximately 2.5 hours. At the beginning of this study session, participants completed resting blood pressure monitoring. They then underwent a tailored cold pressor task to determine the temperature of cold water that would be used for their CPM trials (see below). Next, participants completed standardized self-report measures to assess clinical pain severity, pain interference, pain catastrophizing, as well as depressive symptoms. These measures were followed by completion of a quantitative sensory testing battery which included TS of mechanical and heat pain as well as assessment of CPM. Sociodemographic information was collected from all participants and included age, sex, and racial background, as well as poverty status. Annual household income adjusted for number of occupants was used to determine poverty status according to 2017 guidelines put forth by the U.S. Department of Health and Human Services ("Annual update of the HHS poverty guidelines," 2017).

Telephone Screening of Inclusion/Exclusion Criteria

All interested individuals completed screening via telephone to determine eligibility for study inclusion. PLWH with chronic pain were included in this study only if they reported a pain problem that persisted for at least three months and resulted in pain on at least half the days in the past six months (Treede et al., 2015). Furthermore, PLWH with chronic pain were only included if they denied any type of pain-alleviating surgery within the past year, or pain intervention (e.g., steroid injection) in the past month. PLWH without chronic pain were included in the study only if they denied any ongoing chronic pain problems and also denied any episodes of acute pain within the two weeks prior to study participation. Controls were included in the study only if they denied having any chronic pain condition and were HIV negative to the best of their knowledge. Additional inclusion criteria that needed to be met for all study participants were as follows: no evidence of uncontrolled hypertension (i.e., resting blood pressure > 150/95) assessed via sphygmomanometer during study session. This exclusionary criterion was included to prevent potentially unsafe rises in blood pressure produced by quantitative sensory testing. Also, no circulatory disorders, no history of cardiac events, no history of stroke or seizure, no history of metabolic disease, no ongoing cancer or related treatment, and not currently pregnant. A total of 65 PLWH with chronic pain were screened for study eligibility, while 59 were enrolled. Of the 55 PLWH without chronic pain who were screened for study eligibility, 51 were enrolled. Fifty controls were screened for eligibility and all were enrolled into the study. Of the 10 PLWH who were not enrolled into the study, six were excluded due to uncontrolled hypertension, two for history of stroke, one for congestive heart failure, and one for recent history of cancer.

Medical Record Review

Medical record review was completed to determine whether PLWH were actively being prescribed anti-retroviral therapy (ART), as well as any medications that could potentially affect endogenous pain modulation such as anti-depressants (Bannister & Dickenson, 2016) or analgesics including opioids (Martini et al., 2015; Niesters, Aarts, et al., 2013). Laboratory data including most recent absolute CD4+ T-cell count, a measure of immune status, and most recent plasma HIV viral load were also obtained. Those participants with 50 copies of virus/mL were considered to have a detectable viral load; all others were considered virologically suppressed (i.e., without detectable viral loads). This cutoff (50) was selected due to its clinical relevance as an HIV treatment endpoint (Ryscavage, Kelly, et al., 2014; Sarmati, D'Ettorre, et al., 2015), and also because we have previously shown that even a small amount of detectable HIV in the blood may be sufficient to alter endogenous pain modulation (Goodin et al., 2017).

Study Session

Tailored Cold Pressor.—At the very beginning of each participant's study session, a tailored cold pressor task was completed to determine the intensity of the conditioning stimulus that would be used in the CPM protocol to be completed during the subsequent quantitative sensory testing session. The use of a tailored cold pressor for CPM assessment is consistent with procedures previously published by our research team (Bulls et al., 2015; Owens et al., 2016). This was done by asking participants to fully immerse their non-

dominant hand to the wrist three consecutive times in the cold water maintained at 16°C, 12°C, and 8°C. The water temperatures were maintained ($\pm .05^\circ\text{C}$) by an ARTIC A25 refrigerated bath with an SC150 immersion circulator (ThermoFisher Scientific, USA) that constantly circulated the water to prevent local warming around the submerged hand (Edens & Gil, 1995). Ratings of pain intensity were obtained at 30 seconds and 60 seconds after each immersion. Participants were provided with audio recorded instructions regarding how to rate the intensity of the pain produced by the cold water on a 0–100 numeric rating scale, such that 0 = no pain and 100 = the most intense pain imaginable (Jensen & Karoly, 1992). The maximum duration of each hand immersion was 60 seconds and there was a five-minute rest period between each immersion. Following the tailoring procedure, the cold water temperature that produced a moderately intense pain rating of ~50 (range: 40–60) on the 0–100 numeric rating scale was selected for each participant as the conditioning stimulus for the completion of CPM trials.

Measures

Clinical Pain Severity and Interference.—The Brief Pain Inventory (BPI)-Short Form is an 11-item multidimensional pain scale with demonstrated reliability in patients with neuropathic and musculoskeletal chronic pain conditions (Tan, Jensen, et al., 2004; Zelman, Gore, et al., 2005). The BPI rates the severity of pain as well as the interference of pain. In this study, pain severity was assessed with 4 items asking about worst, least, and average pain in the last 24 hours, as well as current pain “right now”. These items are scored from 0 (no pain) to 10 (worst imaginable pain). Pain interference is the average of 7 items (0 to 10 scale where 10 reflects “completely interferes”) assessing the degree to which pain interferes with mood, physical activity, work/chores, social activity, relations with others, sleep, enjoyment of life. Higher scores suggest greater pain severity and interference, respectively. The BPI used in this study demonstrated good internal consistency (Cronbach’s $\alpha = .89$).

Pain Catastrophizing.—The standard Pain Catastrophizing Scale (PCS) is a 13-item scale that assesses catastrophic thinking in response to pain (Sullivan, Bishop, et al., 1995). The PCS assesses catastrophic pain-related cognitive-emotional processes by asking participants to recall their experiences during a past occurrence of pain. The PCS total score is calculated by summing the 13-item responses. Higher scores on the PCS are indicative of greater pain-related catastrophizing. In the current study, as is typically done in experimental pain studies, the standard PCS was administered before the initiation of quantitative sensory testing and was considered an assessment of individuals’ tendency to engage in pain-related catastrophizing. The PCS total score, calculated by summing the 13-item responses, provides a good index of the catastrophizing construct through the inclusion of the highly correlated subscales of helplessness, rumination, and magnification. Higher scores on the PCS are indicative of greater pain-related catastrophizing. The internal consistency of the PCS in the current study was good (Cronbach’s $\alpha = .85$).

Depressive Symptoms.—The Center for Epidemiological Studies-Depression Scale (CES-D) was used to measure depressive symptoms in this study. This 20-item measure assesses the frequency of experiencing depressive symptoms over the past week (0 – never or rarely, to 3 – most of the time/all the time). Symptoms of depression measured by the

CES-D include negative mood, guilt/worthlessness, helplessness/hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance (Radloff, 1977). This measure has been shown to be reliable and valid in general populations, including when used in HIV and chronic pain populations (Geisser, Roth, et al., 1997; Natamba et al., 2014). Responses are summed (range 0 – 60), with higher scores indicating greater severity of depression. The CES-D measure used in the current study had good internal consistency (Cronbach's $\alpha = .89$).

Quantitative Sensory Testing

PLWH with chronic pain who reported analgesic medication use including opioids were not asked to withhold these medications prior to completion of quantitative sensory testing given that temporary withdrawal from these medications could have affected pain perception. Instead, it was determined that analgesic medication use would be examined and statistically controlled in data analyses. All participants underwent a series of controlled sensory stimulation procedures to assess TS of mechanical and heat pain, as well as CPM (Starkweather et al., 2015). TS of mechanical pain was always assessed prior to TS of heat pain, and the TS procedures were always completed prior to CPM. Before commencing this session, participants were again provided with audio recorded instructions regarding how to rate the intensity of the pain produced by the mechanical and heat TS procedures on the 0–100 numeric rating scale.

Temporal Summation (TS) of Mechanical Pain.—TS of mechanical pain was assessed using a nylon monofilament (Touchtest Sensory Evaluator 6.65) that was calibrated to bend at 300g of pressure. Testing sites included the back of the non-dominant hand and the ipsilateral trapezius, in randomized order. To assess TS of mechanical pain at each site, participants were instructed to provide a verbal 0–100 rating of pain following a single contact of the monofilament. Then, participants were instructed to provide another 0–100 rating of their greatest pain intensity experienced following a series of 10 contacts, which were provided at a rate of one contact per second. This procedure was repeated twice at each anatomical location. Pain ratings for the single and multiple contacts performed at each anatomical location were averaged across the two trials.

Temporal Summation (TS) of Heat Pain.—TS of heat pain was assessed using a Medoc Thermal Sensory Analyzer - II (Medoc, Ltd., Ramat Yishai, Israel) with a 30×30 mm diameter thermode. All participants completed three separate trials for the TS of heat pain procedure using 46°C, 48°C, and 50°C thermal stimuli. The thermode was placed at midline on the volar surface of the non-dominant forearm for the TS of heat pain trials. The thermode was moved approximately 2.5 centimeters up the forearm prior to commencing the second and third trials to prevent sensitization due to repeated testing; there was a 2-minute rest period between each trial. For each trial, sequences of 5 consecutive heat pulses of 1 second duration were delivered with inter-pulse intervals of 2.5 seconds that were 40°C. For the TS of heat pain procedure, participants were asked to rate the intensity of the pain produced by each heat pulse on the 0–100 numeric rating scale.

Conditional Pain Modulation (CPM) Trials.—For this study, CPM was tested on the dominant dorsal forearm and ipsilateral trapezius using algometry (test stimulus) and the cold pressor (conditioning stimulus) according to guidelines published by Yarnitsky and colleagues (Yarnitsky et al., 2010). A handheld algometer (Medoc, Ltd., AlgoMed, Ramat Yishai, Israel) was alternately applied three times at each anatomical location, in counter-balanced fashion, to determine participants' baseline pressure pain thresholds (PPTs) (Ohrbach & Gale, 1989). Participants indicated when the increasing pressure stimulation first became painful, and PPTs were measured in kilopascals (kPa). Following baseline PPT determination, participants underwent a series of four cold pressor immersions that consisted of placing the non-dominant hand, up to the wrist, into the circulating cold water for 1 minute. The cold pressor was maintained at the tailored temperature that produced a moderately painful sensation as determined at the beginning of the study session. Participants were told they could remove their hand from the water at any time; however, none of the participants prematurely removed their hand prior to the allotted 1 minute for any of the four cold pressor immersions. Approximately 30 seconds after initiation of each cold pressor immersion, while the hand was still immersed, the algometer was used to deliver noxious mechanical stimulation to either the dorsal forearm (two CPM trials) or the ipsilateral trapezius (two CPM trials); the site order was randomized. Participants again indicated when the increasing pressure stimulation first became painful, which represented their conditioned PPTs. There was a 2-minute rest period between each CPM trial.

Data Reduction and Analysis

All data were analyzed using SPSS, version 24 (IBM; Chicago, IL). All participants provided complete demographic and quantitative sensory testing data; however, a small portion of missing data existed for some of the self-report measures (< 5%). The missing data did not systematically vary between PLWH with and without chronic pain and controls, so it was deemed to be missing at random. Therefore, a simple data imputation method was completed using the macro for Hot Deck imputation (Myers, 2011). This data imputation method is well validated, readily accepted in the statistical community, and resulted in complete data for all of the study participants. Descriptive data for the sample are reported separately for PLWH with chronic pain, PLWH without chronic pain, and controls as either percentages or as means and standard deviations. Differences in descriptive data across the three study groups were assessed using Chi-square tests for categorical variables and one-way ANOVA for continuous variables. TS of mechanical and heat pain as well as CPM were tested using repeated measures ANOVA with Greenhouse-Geisser corrections. Statistical control variables were included in study analyses as warranted. Multiple comparisons across the three study groups were accounted for using the Holm-Bonferroni procedure to obtain corrected P values (Holm, 1979). Statistical presentation includes the squared partial eta (η_p^2) as a measure of effect size where appropriate, such that $\eta_p^2 = .01$ is considered a small effect, partial $\eta_p^2 = .06$ a medium-sized effect, and $\eta_p^2 = .14$ a large effect. Lastly, associations among study variables were assessed specifically in PLWH with chronic pain using zero-order correlations.

For the correlation analysis, endogenous pain modulation data obtained via TS and CPM testing were transformed into single continuous variables. TS indices for mechanical pain at the hand and trapezius were obtained by subtracting the pain intensity rating following a single contact with the mechanical stimulus from the pain intensity rating following 10 contacts. For the index representing TS of heat pain, pain intensity ratings for the 1st heat pulse were subtracted from pain intensity ratings for the 5th heat pulse. CPM indices were created by subtracting baseline PPTs from conditioned PPTs for both the forearm and trapezius. These indices reflect the change scores for TS of pain as well as CPM (Yarnitsky et al., 2010), and they were subsequently included in the correlation analysis.

RESULTS

Participant characteristics

Participant characteristics are shown in Table 1. All participants were between the ages of 21 to 77 years and self-identified as either Black/African American or White/Caucasian. No other ethnic/racial group expressed interest in being enrolled into the study. Sex/gender ($\chi^2 = 13.48, p = .009$), race ($\chi^2 = 26.10, p < .001$), and poverty status ($\chi^2 = 58.12, p < .001$) each significantly differed across the three study groups. Specifically, a greater proportion of the control group was comprised of women, White/Caucasians, and individuals living above the poverty line in comparison to PLWH with and without chronic pain. Sex/gender, race, and poverty status did not significantly differ between PLWH with and without chronic pain. Age did not significantly differ across study groups ($F_{2,157} = 0.86, p = .425$). Medical records confirmed the HIV seropositive status for all 110 PLWH included in this study, and also revealed that 98% of both groups were actively receiving ART. The mean CD4+ across the entire sample was 668 cells/mL, while the proportion with a detectable viral load (>50 copies/mL) was 25%. Neither CD4+ ($F_{1,108} = 0.26, p = .872$) or the proportion with a detectable viral load ($\chi^2 = 0.19, p = .667$) significantly differed between PLWH with and without chronic pain. Review of medical records also revealed that 46% and 34% of the overall sample was actively being prescribed an anti-depressant or analgesic medication, respectively. The most commonly prescribed class of anti-depressant medication was selective serotonin reuptake inhibitors (48%), followed by atypical anti-depressants (e.g., mirtazapine, trazadone) (26%), serotonin norepinephrine reuptake inhibitors (20%), and tricyclics (6%). The most commonly prescribed analgesics were non-steroidal anti-inflammatory drugs (34%), followed by gabapentinoids (19%), combinations of analgesics (17%), opioids (15%), muscle relaxers (7%), and other (e.g., triptans for migraine) (8%). A significantly smaller proportion of controls were being prescribed anti-depressant ($\chi^2 = 46.92, p < .001$) and analgesic ($\chi^2 = 35.35, p < .001$) medications relative to PLWH with and without chronic pain. The proportion of PLWH with chronic pain actively prescribed anti-depressant medication did not significantly differ from that of PLWH without chronic pain; however, a significantly greater proportion of PLWH with chronic pain were actively prescribed an analgesic medication compared to PLWH without chronic pain. Depressive symptoms ($F_{2,157} = 18.84, p < .000$) and pain catastrophizing ($F_{2,157} = 40.26, p < .000$) both significantly differed across the three study groups, such that PLWH with chronic pain reported greater severity of depressive symptoms and greater pain catastrophizing compared to PLWH without chronic pain and controls. Among PLWH with chronic pain, the most

frequently reported primary pain location was low back (44%), hips/knees (30%), neck (9%), widespread (3+ distinct sites) (9%), shoulder/arm/hand (4%), and feet (4%). Average chronic pain intensity was reportedly 6.4 out of 10, and ranged from 4.6 (least) to 7.2 (worst) over the past 24 hours. At the time of study session, PLWH with chronic pain reported their pain “right now” to be 6.1. Pain interference was suggestive of moderate impact on daily functioning with an average rating of 5.6 out of 10.

Correlations, group differences, and selection of covariates

The purpose of these analyses was to select appropriate covariates for inclusion in subsequent multivariable models. Across the entire sample, Black/African Americans demonstrated greater TS of mechanical pain at the hand ($F_{1,158} = 7.76, p = .006$) and trapezius ($F_{1,158} = 4.36, p = .038$), as well as less CPM at the forearm ($F_{1,158} = 8.32, p = .004$), compared to White/Caucasians. Women and men did not significantly differ on any of the endogenous pain modulatory variables; however, TS of mechanical pain at the hand ($F_{1,158} = 5.23, p = .024$) and trapezius ($F_{1,158} = 6.32, p = .013$) was significantly less for women compared to transgender women. Participants actively prescribed analgesics demonstrated significantly greater TS of mechanical pain at the hand ($F_{1,158} = 9.16, p = .003$) and trapezius ($F_{1,158} = 9.46, p = .002$) compared to those without active analgesic prescriptions, while those actively prescribed anti-depressants demonstrated significantly greater TS of heat pain at 48°C ($F_{1,158} = 5.86, p = .017$) and 50°C ($F_{1,158} = 4.84, p = .029$) as well as significantly less CPM at the forearm ($F_{1,158} = 4.68, p = .032$) compared to those without active anti-depressant prescriptions. Depressive symptoms were significantly correlated with greater TS of mechanical pain at the hand ($r = .16, p = .043$), while pain catastrophizing was significantly correlated with greater TS of heat pain at 48°C ($r = .23, p = .003$) and greater TS of mechanical pain at the hand ($r = .16, p = .043$) and trapezius ($r = .21, p = .008$). Taken together, participants’ race, sex/gender (dummy coded across men, women, and transgender), analgesic and anti-depressant medications, depressive symptoms, and pain catastrophizing were included as covariates in all analyses presented below. Participants’ age, poverty status, CD4+, and viral load were not associated with any endogenous pain modulatory variable and thus not included as covariates in any analyses.

Differences in temporal summation of mechanical pain

For TS of mechanical pain, the pain intensity rating elicited by the first contact with the nylon monofilament was compared to the rating elicited following the series of ten contacts; this was done at both the hand and trapezius. Data representing TS of mechanical pain are presented in Table 2. Adjusted results show that PLWH with chronic pain demonstrated significantly greater TS of mechanical pain at the hand ($F_{2,150} = 5.86, p = .004; \eta_p^2 = .072$) and trapezius ($F_{2,150} = 4.77, p = .011; \eta_p^2 = .060$) in comparison to PLWH without chronic pain and controls. Specifically, the magnitude (i.e., slope) of TS for mechanical pain stimuli was greater at both body sites for PLWH with chronic pain relative to PLWH without chronic pain and controls (Figure 2, panels A and B). Results remained significant after applying the Holm-Bonferroni adjustment. TS of mechanical pain did not significantly differ at either body site between PLWH without chronic pain and controls.

Differences in temporal summation of heat pain

For TS of heat pain, the pain intensity rating elicited by the first heat pulse was compared to the rating elicited by the fifth heat pulse for the 46°C, 48°C, and 50°C stimuli assessed at the non-dominant volar forearm. Data representing TS of heat pain are also presented in Table 2. Adjusted results show that PLWH with chronic pain demonstrated significantly greater TS of heat pain at 46°C ($F_{2,150} = 15.39$, $p < .001$; $\eta_p^2 = .170$) and 48°C ($F_{2,150} = 11.51$, $p < .001$; $\eta_p^2 = .133$) compared to PLWH without chronic pain and controls. Specifically, the magnitude (i.e., slope) of TS for the 46°C and 48°C heat stimuli was greater for PLWH with chronic pain compared to PLWH without chronic pain and controls (Figure 3, panels A and B). Findings remained significant after applying the Holm-Bonferroni adjustment for multiple comparisons. TS of heat pain at 46°C and 48°C did not significantly differ between PLWH without chronic pain and controls. In response to the 50°C stimulus, TS of heat pain did not significantly differ across the three study groups ($F_{2,150} = 1.53$, $p = .220$; $\eta_p^2 = .021$).

However, as can be seen in Figure 3, panel C, ratings of pain intensity in response to each of the five 50°C heat pulses were significantly higher for PLWH with chronic pain compared to PLWH without chronic pain and controls ($F_{2,150} = 8.02$, $p < .001$; $\eta_p^2 = .097$).

Differences in conditioned pain modulation

For CPM, baseline PPTs were compared to conditioned PPTs (i.e., PPTs assessed during concurrent cold pressor application) at both the forearm and trapezius. As demonstrated in Table 3, controls demonstrated significantly greater CPM effects (i.e., the change between baseline and conditioned PPTs) at the forearm ($F_{2,150} = 3.91$, $p = .022$; $\eta_p^2 = .049$) and trapezius ($F_{2,150} = 3.14$, $p = .046$; $\eta_p^2 = .040$) in comparison to PLWH with chronic pain or PLWH without chronic pain. More specifically, controls demonstrated significant CPM effects while both PLWH with and without chronic pain demonstrated a lack of significant CPM effects (Figure 4, panels A and B). Results remained significant after applying the Holm-Bonferroni adjustment. Taken together, this evidence suggests an overall lack of efficient pain inhibition for both PLWH with chronic pain and PLWH without chronic pain. The temperature of the water used to test CPM did not significantly differ across PLWH with and without chronic pain and controls ($\chi^2 = 7.81$, $p = .100$).

Associations among endogenous pain modulatory processes and clinical pain severity

Pearson correlations are shown in the Table 4 and variable associations among only the PLWH with chronic pain. Results revealed that ratings of greater average pain severity on the BPI were significantly correlated with greater TS of mechanical pain at the hand ($r = .298$, $p = .022$) and trapezius ($r = .336$, $p = .009$). None of the other associations between TS, CPM, and the clinical pain severity variables were significant. Pain catastrophizing and depressive symptoms were each consistently and significantly correlated with greater clinical pain severity and greater pain interference.

DISCUSSION

This study examined the endogenous pain modulatory balance of PLWH with chronic pain by including TS and CPM protocols for the assessment of pain inhibitory and facilitatory processes, respectively. Study protocols used for TS and CPM were consistent with commonly recommended methods (Cruz-Almeida & Fillingim, 2014; Yarnitsky et al., 2010; Yarnitsky et al., 2015). PLWH with chronic pain demonstrated pronociceptive endogenous pain modulatory profiles characterized by high facilitation and low inhibition. Specifically, TS of mechanical and heat pain (at 46°C and 48°C) were significantly greater in PLWH with chronic pain compared to PLWH without chronic pain and controls without HIV or chronic pain. There was no evidence of significant CPM for either PLWH with or without chronic pain; therefore, they did not differ from one another in regards to CPM. However, control participants demonstrated significant CPM effects at both the forearm and trapezius. TS of mechanical pain was significantly associated with greater average clinical pain severity for PLWH with chronic pain. Taken together, our results lend support to the idea that alterations in endogenous pain modulatory processes may be an important contributor to the development and/or experience of chronic pain for PLWH. For both mechanical and heat TS, PLWH with chronic pain reported significantly greater pain in response to the final stimulus application compared to the first despite the stimulus intensity remaining the same across each respective procedure. TS of pain has been a widely incorporated test of pronociceptive endogenous pain facilitation in previous studies (Yarnitsky, 2015); however, no published study to date has examined TS of pain in PLWH with chronic pain. The enhanced endogenous pain facilitation (i.e., TS of pain) found in our study may be indicative of central nervous system (CNS) sensitization (Woolf, 2011). This is because endogenous pain facilitatory pathways are particularly important in initiating and maintaining CNS sensitization (Latremoliere & Woolf, 2009). Our group has previously shown that PLWH report decreased pain thresholds, decreased pain tolerances, and increased pain responses to experimental noxious stimuli consistent with CNS sensitization (Goodin et al., 2017). Chronic pain is maintained in part by CNS sensitization, which refers to a phenomenon of synaptic plasticity and increased neuronal responsiveness in central pain pathways after painful insults. Mounting evidence suggests that the pronociceptive endogenous pain facilitatory processes that initiate and maintain CNS sensitization are driven by neuroinflammation in the peripheral and central nervous system (Ji, Nackley, et al., 2018). Sustained release of cytokines and chemokines in the CNS may promote sensitization by tipping the endogenous pain modulatory balance in the pronociceptive direction (i.e., by promoting pain facilitation while abating pain inhibition). Such a cascade of events is particularly relevant for PLWH because pre-clinical and clinical studies have shown that envelope proteins such as GP120, found on the surface of HIV, initiate neuroinflammation by activating astrocytes and microglia in the CNS (Holguin et al., 2004; Yuan et al., 2014).

That TS of mechanical pain, but not TS of heat pain, was significantly associated with greater average clinical pain severity for PLWH with chronic pain is consistent with findings from previous studies conducted by our group in patients with chronically painful musculoskeletal conditions including knee osteoarthritis (Goodin et al., 2014) and low back pain (Owens et al., 2016). In the current study, low back (44%) and hips/knees (30%)

represented almost three quarters of the primary pain locations reported by PLWH with chronic pain. Given the presumed musculoskeletal origin of this chronic pain, the clinical pain experiences of PLWH are possibly mechanically evoked (e.g., trunk flexion, postural perturbations, gait alterations) (Griffith et al., 2012). Therefore, the mechanical stimuli used to test TS of pain may be more clinically relevant than other modalities such as heat. Given that we have now demonstrated TS of mechanical pain, but not TS of heat pain, to be associated with clinical pain severity across three entirely different studies including this one with PLWH, a potential clinical application for TS of mechanical pain is becoming increasingly apparent. The simple procedure for assessing TS of mechanical pain in this study could easily be included in clinical practice to help identify patients with amplified pain sensitivity who may require a more intensive, multidisciplinary approach to their chronic pain management. Unlike TS of heat pain assessment, which requires costly equipment and methodologies that are technically elaborate and time consuming, TS of mechanical pain assessment with a nylon monofilament is relatively brief, inexpensive, and requires minimal technical expertise (Goodin et al., 2014).

Our hypothesis that PLWH with chronic pain would demonstrate less efficient CPM compared to PLWH without chronic pain and controls was partially supported. The concurrent cold pressor pain had a significant conditioning effect on pressure pain thresholds for controls, which is indicative of efficient endogenous pain inhibition for individuals without HIV or chronic pain. Conversely, PLWH with chronic pain did not demonstrate any conditioning effect of the cold pressor on their pressure pain thresholds, which suggests an absolute lack of endogenous pain inhibition (i.e., CPM). Lack of CPM in PLWH with chronic pain was expected and consistent with our first hypothesis. However, contrary to what was hypothesized, PLWH without chronic pain also demonstrated lack of a significant CPM effect. This lack of CPM effect in PLWH without chronic pain may represent a risk factor for the future development of chronic pain. Recent findings suggest that diminished endogenous inhibitory control is likely to be an important element in determining whether pain becomes chronic (Ossipov et al., 2014). The inability to engage a robust endogenous pain inhibitory system may leave PLWH vulnerable and susceptible to a chronic pain condition.

It is noteworthy that PLWH with chronic pain reported more catastrophic thoughts about pain and depressive symptoms than PLWH without chronic pain and controls. Furthermore, findings from the correlational analysis also revealed that pain catastrophizing and depressive symptoms were each significantly associated with greater clinical pain severity (e.g., worst pain, least pain, pain right now) and greater pain interference for PLWH with chronic pain. This finding is consistent with previous work whereby pain catastrophizing and depression were shown to be correlated with increased pain-related disability and ART side-effects, respectively, in PLWH with painful neuropathy (Lucey et al., 2011). Negative thoughts about pain, including helplessness and thoughts similar to catastrophizing, have been associated with interference in daily functional activities, overall emotional distress, and affective symptoms in HIV patients reporting neuropathic pain (Evans, Weinberg, et al., 2003; Griswold, Evans, et al., 2005). Taken together, initial evidence suggests that pain catastrophizing and depression are likely related to poor clinical pain outcomes in PLWH. Although not directly supported in the current study, prior work has also demonstrated that

pain catastrophizing and depression are associated with enhanced endogenous pain facilitation and dampened pain inhibition (Goodin et al., 2013; Goodin et al., 2009; Nahman-Averbuch, Nir, et al., 2016; Rhudy et al., 2011). For this reason, pain catastrophizing and depression have been described as psychological risk factors associated with alterations in endogenous pain facilitatory and inhibitory processes that maintain or aggravate CNS sensitization (Quartana, Campbell, et al., 2009; van Wilgen et al., 2018). Importantly, cognitive-behavioral therapies for chronic pain management have been shown to be effective for mitigating the negative effects of pain catastrophizing and depression (Ehde, Dillworth, et al., 2014). Whether such psychologically-based therapies might improve chronic pain and related CNS sensitization for PLWH by diminishing pain catastrophizing and depressive symptoms is a topic for further research.

Several limitations should be considered when evaluating the findings of this study. First, interpretation of the clinical relevance of this study is limited by the cross-sectional nature of the study design. At this time, we cannot determine whether the alterations in endogenous pain modulatory processes presented in this study were a determinant or consequence of chronic pain development in PLWH. Future longitudinal studies are needed to determine whether enhanced endogenous pain facilitation and/or diminished pain inhibition predict the development of chronic pain in PLWH. Second, although the classification of chronic pain used in this study conformed to the recently published standards put forth by the International Association for the Study of Pain Task Force for the Classification of Chronic Pain (Treede et al., 2015), we did not systematically obtain information related to potential pathoanatomical underpinnings of chronic pain in PLWH (e.g., avascular necrosis, small fiber neuropathy, non-specific). Thus, different etiological underpinnings for chronic pain may have been present in this sample, and it is unclear whether this potentially impacted tests of endogenous pain modulatory processes. Third, the alterations in endogenous pain modulatory processes presented in this study are consistent with previous findings observed in non-HIV samples with chronic pain conditions including fibromyalgia (O'Brien, Deitos, et al., 2018), osteoarthritis (King et al., 2013), and irritable bowel syndrome (Piche, Arseneault, et al., 2010), among others. It is not possible to determine from the current study whether HIV promotes chronic pain by playing a specific role in altering these endogenous pain modulatory processes, or whether alterations in endogenous pain modulatory mechanisms represents a shared chronic pain correlate across populations with and without HIV. Additional research in humans is needed to determine whether HIV might specifically alter endogenous pain modulatory processes through the purported proliferation of neuroinflammation, for example. Lastly, controls were asked to self-report their negative HIV status; however, we did not confirm this with blood tests.

In conclusion, the findings from this study provide novel evidence for an endogenous pain modulatory balance that is associated with the promotion of chronic pain in PLWH when dynamic tests of TS (facilitation) and CPM (inhibition) are used. The findings lend support to an endogenous pain modulatory balance characterized by enhanced pain facilitatory processes assessed via TS of mechanical and heat stimuli, as well as diminished pain inhibitory processes tested via CPM methodology. TS of mechanical pain may have particular clinical relevance for PLWH, given associations with average clinical pain severity found in this study and others conducted by our group. Additionally, PLWH with chronic

pain reported greater pain catastrophizing and depressive symptoms compared to PLWH without chronic pain. Evidence suggests that pain catastrophizing and depression are important psychological factors associated with increased disability in chronic pain populations (Arnow et al., 2006; Quartana et al., 2009). Thus, it will be important moving forward for clinically-focused research and treatment to address the mental, as well as physical, health of PLWH with chronic pain.

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REFERENCES

- Annual update of the HHS poverty guidelines. (2017). Department of Health and Human Services, <https://aspe.hhs.gov/2017-poverty-guidelines>, Accessed June 21, 2018.
- Arnow BA, Hunkeler EM, Blasey CM, Lee J, Constantino MJ, Fireman B, ... Hayward C (2006). Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med*, 68(2), 262–268. doi:10.1097/01.psy.0000204851.15499.fc [PubMed: 16554392]
- Bannister K, & Dickenson AH (2016). What do monoamines do in pain modulation? *Curr Opin Support Palliat Care*, 10(2), 143–148. doi:10.1097/SPC.0000000000000207 [PubMed: 27043287]
- Bulls HW, Freeman EL, Anderson AJ, Robbins MT, Ness TJ, & Goodin BR (2015). Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *J Pain Res*, 8, 311–320. doi:10.2147/JPR.S84607 [PubMed: 26170713]
- Cruz-Almeida Y, & Fillingim RB (2014). Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med*, 15(1), 61–72. doi:10.1111/pme.12230 [PubMed: 24010588]
- Dalakas MC (2001). Peripheral neuropathy and antiretroviral drugs. *J Peripher Nerv Syst*, 6(1), 14–20. [PubMed: 11293802]
- Dobalian A, Tsao JC, & Duncan RP (2004). Pain and the use of outpatient services among persons with HIV: results from a nationally representative survey. *Med Care*, 42(2), 129–138. doi: 10.1097/01.mlr.0000108744.45327.d4 [PubMed: 14734950]
- Edens JL, & Gil KM (1995). Experimental induction of pain: Utility in the study of clinical pain. *Behav Ther*, 26, 197–216.
- Ehde DM, Dillworth TM, & Turner JA (2014). Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol*, 69(2), 153–166. doi: 10.1037/a0035747 [PubMed: 24547801]
- Eide PK (2000). Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain*, 4(1), 5–15. doi:10.1053/eujp.1999.0154 [PubMed: 10833550]
- Evans S, Weinberg BA, Spielman L, & Fishman B (2003). Assessing negative thoughts in response to pain among people with HIV. *Pain*, 105(1–2), 239–245. [PubMed: 14499441]
- Gabbai AA, Castelo A, & Oliveira AS (2013). HIV peripheral neuropathy. *Handb Clin Neurol*, 115, 515–529. doi:10.1016/B978-0-444-52902-2.00029-1 [PubMed: 23931799]
- Geisser ME, Roth RS, & Robinson ME (1997). Assessing depression among persons with chronic pain using the Center for Epidemiological Studies-Depression Scale and the Beck Depression Inventory: a comparative analysis. *Clin J Pain*, 13(2), 163–170. [PubMed: 9186024]
- Goodin BR, Bulls HW, Herbert MS, Schmidt J, King CD, Glover TL, ... Fillingim RB (2014). Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosom Med*, 76(4), 302–310. doi: 10.1097/PSY.0000000000000058 [PubMed: 24804882]

- Goodin BR, Glover TL, Sotolongo A, King CD, Sibille KT, Herbert MS, ... Fillingim RB (2013). The association of greater dispositional optimism with less endogenous pain facilitation is indirectly transmitted through lower levels of pain catastrophizing. *J Pain*, 14(2), 126–135. doi:10.1016/j.jpain.2012.10.007 [PubMed: 23218934]
- Goodin BR, McGuire L, Allshouse M, Stapleton L, Haythornthwaite JA, Burns N, ... Edwards RR (2009). Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. *J Pain*, 10(2), 180–190. doi:10.1016/j.jpain.2008.08.012 [PubMed: 19010738]
- Goodin BR, Owens MA, Yessick LR, Rainey RL, Okunbor JI, White DM, ... Merlin JS (2017). Detectable Viral Load May Be Associated with Increased Pain Sensitivity in Persons Living with HIV: Preliminary Findings. *Pain Med*, 18(12), 2289–2295. doi:10.1093/pm/pnx057 [PubMed: 28398572]
- Granovsky Y, & Yarnitsky D (2013). Personalized pain medicine: the clinical value of psychophysical assessment of pain modulation profile. *Rambam Maimonides Med J*, 4(4), e0024. doi:10.5041/RMMJ.10131 [PubMed: 24228167]
- Griffith LE, Shannon HS, Wells RP, Walter SD, Cole DC, Cote P, ... Langlois LE (2012). Individual participant data meta-analysis of mechanical workplace risk factors and low back pain. *Am J Public Health*, 102(2), 309–318. doi:10.2105/AJPH.2011.300343 [PubMed: 22390445]
- Griswold GA, Evans S, Spielman L, & Fishman B (2005). Coping strategies of HIV patients with peripheral neuropathy. *AIDS Care*, 17(6), 711–720. doi:10.1080/09540120412331336715 [PubMed: 16036257]
- Heinricher MM, Tavares I, Leith JL, & Lumb BM (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev*, 60(1), 214–225. doi:10.1016/j.brainresrev.2008.12.009 [PubMed: 19146877]
- Holguin A, O'Connor KA, Biedenkapp J, Campisi J, Wieseler-Frank J, Milligan ED, ... Watkins LR (2004). HIV-1 gp120 stimulates proinflammatory cytokine-mediated pain facilitation via activation of nitric oxide synthase-I (nNOS). *Pain*, 110(3), 517–530. doi:10.1016/j.pain.2004.02.018 [PubMed: 15288392]
- Holm S (1979). A simple sequentially rejective multiple test procedure. *Scand J Statist*, 6, 65–70.
- Jensen MP, & Karoly P (1992). Self-report scales and procedures for assessing pain in adults In Turk DC & Melzack R (Eds.), *Handbook of pain assessment* (pp. 135–151). New York, NY: Guilford Press.
- Ji RR, Nackley A, Huh Y, Terrando N, & Maixner W (2018). Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. *Anesthesiology*. doi:10.1097/ALN.0000000000002130
- Jiao JM, So E, Jebakumar J, George MC, Simpson DM, & Robinson-Papp J (2016). Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization. *Pain*, 157(4), 931–937. doi:10.1097/j.pain.0000000000000462 [PubMed: 26683238]
- King CD, Sibille KT, Goodin BR, Cruz-Almeida Y, Glover TL, Bartley E, ... Fillingim RB (2013). Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthritis Cartilage*, 21(9), 1243–1252. doi:10.1016/j.joca.2013.05.015 [PubMed: 23973137]
- Latremoliere A, & Woolf CJ (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*, 10(9), 895–926. doi:10.1016/j.jpain.2009.06.012 [PubMed: 19712899]
- Le Bars D (2002). The whole body receptive field of dorsal horn multireceptive neurones. *Brain Res Brain Res Rev*, 40(1–3), 29–44. [PubMed: 12589904]
- Lucey BP, Clifford DB, Creighton J, Edwards RR, McArthur JC, & Haythornthwaite J (2011). Relationship of depression and catastrophizing to pain, disability, and medication adherence in patients with HIV-associated sensory neuropathy. *AIDS Care*, 23(8), 921–928. doi:10.1080/09540121.2010.543883 [PubMed: 21500021]
- Magerl W, Wilk SH, & Treede RD (1998). Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain*, 74(2–3), 257–268. [PubMed: 9520240]
- Martini C, van Velzen M, Drewes A, Aarts L, Dahan A, & Niesters M (2015). A Randomized Controlled Trial on the Effect of Tapentadol and Morphine on Conditioned Pain Modulation in

- Healthy Volunteers. PLoS One, 10(6), e0128997. doi:10.1371/journal.pone.0128997 [PubMed: 26076171]
- Merlin JS, Cen L, Praestgaard A, Turner M, Obando A, Alpert C, ... Frank I (2012). Pain and physical and psychological symptoms in ambulatory HIV patients in the current treatment era. *J Pain Symptom Manage*, 43(3), 638–645. doi:10.1016/j.jpainsymman.2011.04.019 [PubMed: 22115794]
- Merlin JS, Long D, Becker WC, Cachay ER, Christopolous KA, Claborn K, ... Gross R (2018). The Association of Chronic Pain and Long-Term Opioid Therapy with HIV Treatment Outcomes. *J Acquir Immune Defic Syndr*. doi:10.1097/QAI.0000000000001741
- Merlin JS, Westfall AO, Chamot E, Overton ET, Willig JH, Ritchie C, ... Mugavero MJ (2013). Pain is independently associated with impaired physical function in HIV-infected patients. *Pain Med*, 14(12), 1985–1993. doi:10.1111/pme.12255 [PubMed: 24119077]
- Merlin JS, Westfall AO, Raper JL, Zinski A, Norton WE, Willig JH, ... Mugavero MJ (2012). Pain, mood, and substance abuse in HIV: implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. *J Acquir Immune Defic Syndr*, 61(2), 164–170. doi:10.1097/QAI.0b013e3182662215 [PubMed: 22766967]
- Miaskowski C, Penko JM, Guzman D, Mattson JE, Bangsberg DR, & Kushel MB (2011). Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection. *J Pain*, 12(9), 1004–1016. doi:10.1016/j.jpain.2011.04.002 [PubMed: 21684218]
- Myers TA (2011). Goodbye listwise deletion: Presenting hotdeck imputation as an easy and effective tool for handling missing data. *Communication Measures & Methods*, 5, 297–310.
- Nahman-Averbuch H, Nir RR, Sprecher E, & Yarnitsky D (2016). Psychological Factors and Conditioned Pain Modulation: A Meta-Analysis. *Clin J Pain*, 32(6), 541–554. doi:10.1097/AJP.0000000000000296 [PubMed: 26340657]
- Natamba BK, Achan J, Arbach A, Oyok TO, Ghosh S, Mehta S, ... Young SL (2014). Reliability and validity of the center for epidemiologic studies-depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda: a cross-sectional study. *BMC Psychiatry*, 14, 303. doi:10.1186/s12888-014-0303-y [PubMed: 25416286]
- Niesters M, Aarts L, Sarton E, & Dahan A (2013). Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth*, 110(6), 1010–1016. doi:10.1093/bja/aes578 [PubMed: 23384733]
- Nir RR, & Yarnitsky D (2015). Conditioned pain modulation. *Curr Opin Support Palliat Care*, 9(2), 131–137. doi:10.1097/SPC.0000000000000126 [PubMed: 25699686]
- O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, & Carrillo-de-la-Pena MT (2018). Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *J Pain*. doi:10.1016/j.jpain.2018.01.010
- O'Donnell LA, Agrawal A, Jordan-Sciutto KL, Dichter MA, Lynch DR, & Kolson DL (2006). Human immunodeficiency virus (HIV)-induced neurotoxicity: roles for the NMDA receptor subtypes. *J Neurosci*, 26(3), 981–990. doi:10.1523/JNEUROSCI.4617-05.2006 [PubMed: 16421318]
- Ohrbach R, & Gale EN (1989). Pressure pain thresholds in normal muscles: reliability, measurement effects, and topographic differences. *Pain*, 37(3), 257–263. [PubMed: 2755707]
- Ossipov MH (2012). The perception and endogenous modulation of pain. *Scientifica (Cairo)*, 2012, 561761. doi:10.6064/2012/561761 [PubMed: 24278716]
- Ossipov MH, Dussor GO, & Porreca F (2010). Central modulation of pain. *J Clin Invest*, 120(11), 3779–3787. doi:10.1172/JCI43766 [PubMed: 21041960]
- Ossipov MH, Morimura K, & Porreca F (2014). Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*, 8(2), 143–151. doi:10.1097/SPC.0000000000000055 [PubMed: 24752199]
- Owens MA, Bulls HW, Trost Z, Terry SC, Gossett EW, Wesson-Sides KM, & Goodin BR (2016). An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Med*, 17(8), 1452–1464. doi:10.1093/pm/pnv074 [PubMed: 26814298]
- Parker R, Stein DJ, & Jelsma J (2014). Pain in people living with HIV/AIDS: a systematic review. *J Int AIDS Soc*, 17, 18719. doi:10.7448/IAS.17.1.18719 [PubMed: 24560338]

- Piche M, Arsenault M, Poitras P, Rainville P, & Bouin M (2010). Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome. *Pain*, 148(1), 49–58. doi: 10.1016/j.pain.2009.10.005 [PubMed: 19889500]
- Price DD, Hu JW, Dubner R, & Gracely RH (1977). Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*, 3(1), 57–68. [PubMed: 876667]
- Quartana PJ, Campbell CM, & Edwards RR (2009). Pain catastrophizing: a critical review. *Expert Rev Neurother*, 9(5), 745–758. doi:10.1586/ern.09.34 [PubMed: 19402782]
- Radloff LS (1977). A self-report depression scale for research in the general population. *Applied Psychological measurement*, 1(3), 385–401.
- Rhudy JL, Martin SL, Terry EL, France CR, Bartley EJ, DelVentura JL, & Kerr KL (2011). Pain catastrophizing is related to temporal summation of pain but not temporal summation of the nociceptive flexion reflex. *Pain*, 152(4), 794–801. doi:10.1016/j.pain.2010.12.041 [PubMed: 21316150]
- Ryscavage P, Kelly S, Li JZ, Harrigan PR, & Taiwo B (2014). Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. *Antimicrob Agents Chemother*, 58(7), 3585–3598. doi:10.1128/AAC.00076-14 [PubMed: 24733471]
- Sarmati L, D'Ettorre G, Parisi SG, & Andreoni M (2015). HIV Replication at Low Copy Number and its Correlation with the HIV Reservoir: A Clinical Perspective. *Curr HIV Res*, 13(3), 250–257. [PubMed: 25845389]
- Spudich S, & Gonzalez-Scarano F (2012). HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. *Cold Spring Harb Perspect Med*, 2(6), a007120. doi: 10.1101/cshperspect.a007120 [PubMed: 22675662]
- Starkweather AR, Heinemann AW, Storey S, Rubia G, Lyon DE, Greenspan JD, & Dorsey SG (2015). Methods to measure peripheral and central pain sensitization using quantitative sensory testing: A focus on individuals with low back pain. *Applied Nursing Research*, e-pub ahead of print.
- Staud R (2012). Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother*, 12(5), 577–585. doi:10.1586/ern.12.41 [PubMed: 22550986]
- Staud R (2013). The important role of CNS facilitation and inhibition for chronic pain. *Int J Clin Rheumatol*, 8(6), 639–646. doi:10.2217/ijr.13.57 [PubMed: 24489609]
- Staud R, Vierck CJ, Cannon RL, Mauderli AP, & Price DD (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain*, 91(1–2), 165–175. [PubMed: 11240089]
- Staud R, Weyl EE, Riley JL, 3rd, & Fillingim RB (2014). Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. *PLoS One*, 9(2), e89086. doi:10.1371/journal.pone.0089086 [PubMed: 24558475]
- Sullivan MJL, Bishop SR, & Pivik J (1995). The pain catastrophizing scale: development and validation. *Psychological Assessment*, 7(4), 524.
- Tan G, Jensen MP, Thornby JL, & Shanti BF (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*, 5(2), 133–137. doi:10.1016/j.jpain.2003.12.005 [PubMed: 15042521]
- Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, ... Wang SJ (2015). A classification of chronic pain for ICD-11. *Pain*, 156(6), 1003–1007. doi:10.1097/j.pain.000000000000160 [PubMed: 25844555]
- van Wilgen CP, Vuijk PJ, Kregel J, Voogt L, Meeus M, Descheemaeker F, ... Nijs J (2018). Psychological Distress and Widespread Pain Contribute to the Variance of the Central Sensitization Inventory: A Cross-Sectional Study in Patients with Chronic Pain. *Pain Pract*, 18(2), 239–246. doi:10.1111/papr.12600 [PubMed: 28449376]
- Woolf CJ (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, 152(3 Suppl), S2–15. doi:10.1016/j.pain.2010.09.030 [PubMed: 20961685]
- Yarnitsky D (2015). Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain*, 156 Suppl 1, S24–31. doi:10.1097/01.jpain.0000460343.46847.58 [PubMed: 25789433]
- Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, ... Wilder-Smith O (2010). Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain*, 14(4), 339. doi:10.1016/j.ejpain.2010.02.004 [PubMed: 20227310]

- Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, ... Wilder-Smith OH (2015). Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain*, 19(6), 805–806. doi:10.1002/ejp.605 [PubMed: 25330039]
- Yarnitsky D, Granot M, & Granovsky Y (2014). Pain modulation profile and pain therapy: between pro- and antinociception. *Pain*, 155(4), 663–665. doi:10.1016/j.pain.2013.11.005 [PubMed: 24269491]
- Yuan SB, Shi Y, Chen J, Zhou X, Li G, Gelman BB, ... Tang SJ (2014). Gp120 in the pathogenesis of human immunodeficiency virus-associated pain. *Ann Neurol*, 75(6), 837–850. doi:10.1002/ana.24139 [PubMed: 24633867]
- Zelman DC, Gore M, Dukes E, Tai KS, & Brandenburg N (2005). Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. *J Pain Symptom Manage*, 29(4), 401–410. doi:10.1016/j.jpainsymman.2004.06.018 [PubMed: 15857744]

Figure 1:
Flow diagram representing matriculation of participants through the study.

Figure 2:
Differences in temporal summation of mechanical pain at the hand (A) and the trapezius (B) between PLWH with and without chronic pain (CP) and controls.

Figure 3:
Differences in temporal summation of heat pain at 46°C (A), 48°C (B), and 50°C (C) between PLWH with and without chronic pain (CP) and controls.

Figure 4: Differences in conditioned pain modulation at the forearm (A) and trapezius (B) between PLWH with and without chronic pain (CP) and controls.

Table 1:**Participant Characteristics**

	Controls (N = 50)	PLWH without Chronic Pain (N = 51)	PLWH with Chronic Pain (N = 59)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %
<u>Demographic Characteristics</u>			
Age - years	49.1 (12.1)	46.3 (10.2)	47.3 (9.2)
Gender			
Men	44%	65%	52%
Women	56%	35%	39%
Transgender	0%	0%	9%
Race			
non-Hispanic Black	52%	82%	93%
non-Hispanic White	48%	18%	7%
Poverty			
Below Poverty Line	24%	84%	87%
Above Poverty Line	76%	16%	13%
<u>Clinical Characteristics</u>			
Most Recent CD4+ (cells/mL)	---	674 (432)	663 (335)
Viral load (>50 copies/mL)			
Undetectable	---	76%	73%
Detectable	---	24%	27%
Anti-Retroviral Therapy (ART)			
Actively Prescribed	---	98%	98%
Not Prescribed	---	2%	2%
Anti-Depressant			
Actively Prescribed	6%	59%	68%
Not Prescribed	94%	41%	32%
Analgesic			
Actively Prescribed	8%	27%	61%
Not Prescribed	92%	73%	39%
CES-D - Depressive Symptoms	13.5 (10.0)	14.9 (10.1)	24.6 (11.1)
PCS - Pain Catastrophizing	8.9 (7.7)	15.9 (10.6)	26.7 (12.2)
BPI - Worst Pain	---	---	7.2 (2.2)
BPI - Least Pain	---	---	4.6 (2.6)
BPI - Average Pain	---	---	6.4 (2.2)
BPI - Pain Right Now	---	---	6.1 (2.9)
BPI - Pain Interference	---	---	5.6 (2.5)

Note: CES-D = Center for Epidemiological Studies Depression Scale; PCS = Pain Catastrophizing Scale; BPI = Brief Pain Inventory.

Table 2:

Temporal summation (TS) of mechanical and heat pain according to ratings of pain intensity on the 0 – 100 numeric rating scale.

		Controls Mean (SD)	PLWH without Chronic Pain Mean (SD)	PLWH with Chronic Pain Mean (SD)
TS of mechanical pain				
Hand				
	1 Contact	4.31 (6.63)	1.71 (3.54)	7.08 (9.27)
	10 Contacts	10.40 (11.05)	5.36 (8.51)	23.21 (25.31)
Trapezius				
	1 Contact	3.98 (5.28)	2.95 (6.25)	7.39 (9.55)
	10 Contacts	11.75 (12.91)	8.08 (12.99)	25.84 (25.74)
TS of heat pain				
46°C				
	1 st Pulse	29.96 (25.53)	38.10 (30.10)	50.47 (32.08)
	5 th Pulse	25.54 (24.83)	37.25 (30.12)	64.36 (33.39)
48°C				
	1 st Pulse	36.88 (24.78)	46.43 (32.11)	65.31 (32.42)
	5 th Pulse	31.96 (24.12)	49.47 (34.90)	82.49 (27.12)
50°C				
	1 st Pulse	42.40 (26.29)	53.01 (33.81)	73.54 (31.55)
	5 th Pulse	46.92 (25.42)	65.01 (34.78)	86.46 (25.03)

Note: 1 Contact = pain intensity rating in response to first contact with mechanical stimuli, 10 contact = pain intensity rating in response to 10 contacts with mechanical stimuli; 1st pulse = pain intensity rating for first heat pulse, 5th pulse = pain intensity rating for 5th heat pulse.

Table 3:

Baseline and conditioned pressure pain thresholds (PPTs) to determine conditioned pain modulation (CPM) at the forearm and trapezius

	Controls Mean (SD)	PLWH without Chronic Pain Mean (SD)	PLWH with Chronic Pain Mean (SD)
Forearm			
Baseline PPTs	404.30 (189.92)	348.45 (177.50)	272.77 (123.47)
Conditioned PPTs	503.71 (217.93)	359.25 (176.97)	307.68 (150.08)
Trapezius			
Baseline PPTs	458.10 (242.68)	351.93 (204.86)	297.42 (151.05)
Conditioned PPTs	551.91 (249.05)	384.72 (203.83)	326.24 (154.89)

Note: All PPT scores are presented as kilopascals (kPa).

Correlations among endogenous pain modulatory processes and clinical pain severity, as well as pain interference, depressive symptoms, and pain catastrophizing among PLWH with chronic pain

Table 4:

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. BPI - average pain	—												
2. BPI - worst pain	.545**	—											
3. BPI - least pain	.630**	.606**	—										
4. BPI - pain right now	.594**	.610**	.703**	—									
5. BPI - pain interference	.510**	.623**	.605**	.542**	—								
6. TS mechanical - hand	.298**	.176	.111	.034	.082	—							
7. TS mechanical - trapezius	.336**	.158	.209	.183	.155	.707**	—						
8. TS heat - 46°C	.216	-.055	.044	.044	.036	.064	.016	—					
9. TS heat - 48°C	.145	-.134	-.026	.057	-.013	-.158	-.033	.317*	—				
10. TS heat - 50°C	.084	-.091	.001	.056	.058	-.055	-.050	.090	.587**	—			
11. CPM - forearm	-.202	-.012	-.149	-.062	-.121	-.022	-.128	-.260*	-.020	.057	—		
12. CPM - trapezius	.113	.138	.117	.091	.087	.054	.054	-.007	-.082	.091	.091	—	
13. CES-D	.223	.262*	.318*	.261*	.426**	.026	-.005	-.120	-.291*	.026	.104	-.005	—
14. PCS	.261*	.299*	.366**	.443**	.470**	-.076	.028	.045	.026	.189	.081	.002	.712**

* = $p < .05$,

** = $p < .01$

Note: BPI = Brief Pain Inventory; TS = temporal summation; CPM = conditioned pain modulation; CES-D = Center for Epidemiological Studies – Depression Scale; PCS = Pain Catastrophizing Scale.