Running Title: Aging effects on TS and CPM

The decline of endogenous pain modulation with aging: A meta-analysis of temporal summation and conditioned pain modulation

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Highlights

- Older compared to younger adults showed enhanced temporal summation of pain.
- Older compared to younger adults exhibited deficient conditioned pain modulation.
- The decline in endogenous pain modulation potentially starts in middle-age.
- Different experimental methods across studies lead to variability in effect sizes.

Abstract

The purpose of this article was to examine age-related changes in conditioned pain modulation (CPM) and temporal summation of pain (TS) using meta-analytic techniques. Five electronic databases were searched for studies that compared measures of CPM and TS between healthy, chronic pain-free younger, middle-aged, and older adults. Eleven studies were included in the final review for TS and 11 studies were included in the review of CPM. The results suggested a moderate magnitude of difference in TS between younger adults and middle-aged/older adults, with the older cohorts exhibiting enhanced TS of pain. Considerable variability existed in the magnitude of the effects sizes, which was likely due to the different experimental methodology used across studies (i.e., inter-stimulus interval, stimulus type, body location). In regards to CPM, the data revealed a large magnitude of difference between younger and older adults, with younger adults exhibiting more efficient pain inhibition. Differences in CPM between middle-aged and older adults were minimal. The magnitude of pain inhibition during CPM in older adults may depend on the use of concurrent vs. non-concurrent protocols. In summary, the data provided strong quantitative evidence of a general age-related decline in endogenous pain modulatory function as measured by TS and CPM.

PERSPECTIVE: *This review compared conditioned pain modulation and temporal summation of pain between younger, middle-aged, and older adults. These findings enhance our understanding of the decline in endogenous pain modulatory function associated with normal aging.*

KEYWORDS: aging, pain modulation, meta-analysis, temporal summation, conditioned pain modulation

Introduction

The prevalence estimates of chronic pain among older adults in the United States are alarming, with estimates as high as 60% to 75% among community-dwelling older adults [43]. Furthermore, epidemiological research shows that the prevalence of chronic pain increases with age up to the seventh decade of life and then plateaus [14]. A growing body of evidence suggests one potential mechanism predisposing older adults to increased risk of chronic pain is an age-related decline in the capacity to endogenously modulate pain. Animal research suggests that aging is associated with sensitization of central pain pathways [47] and a decline in endogenous pain inhibition involving opioidergic and serotonergic systems [8]. In humans, the two most common quantitative sensory tests used to assess endogenous pain inhibitory function and endogenous pain facilitatory processes are conditioned pain modulation (CPM) and temporal summation (TS), respectively [41]. CPM is based on a "pain inhibits pain" model in which a painful stimulus at one body part (conditioning stimulus) reduces pain perception to another painful stimulus (test stimulus) at a distant body part [45]. Temporal summation of pain severity is the behavioral correlate of the "wind-up" of spinal wide dynamic range neurons of the dorsal horn [35; 36]. This test typically involves the delivery of repetitive noxious stimuli at a constant intensity and measuring the degree of pain facilitation across the stimuli. Poor pain inhibitory capacity on the CPM test and enhanced pain facilitation on the TS test indirectly indicate the presence of central sensitization, which increases the susceptibility for chronic pain. Indeed, enhanced TS and inefficient CPM are characteristic of many chronic pain conditions [21; 32], associated with increased reports of clinical pain severity in healthy adults [4; 6], and predict the transition from acute to chronic pain following surgery [46].

In the past two decades a multitude of studies have been published examining age-related differences in TS and CPM. Many of these studies show that older adults free of

chronic pain exhibit inefficient pain inhibition on the CPM test compared younger adults [5; 17; 39; 44]. However, discrepancies exist between studies with some indicating older adults exhibit pain facilitation rather than inhibition during CPM protocols [39], some showing pain inhibition in younger and older age groups with diminished inhibition in older cohorts [44], and one study showing similar pain inhibition between older and younger adults [28]. Similarly, the literature on age differences in TS of pain includes substantial variability in both methods and results. Many studies show older adults exhibit greater pain facilitation on the TS test [7; 18]; however, the presence of age differences have depended on TS protocol parameters such as the inter-stimulus interval (ISI), the location (e.g. hand, arm, leg) of stimulation, or the type of stimulus (e.g. heat, pressure, electric). Thus, a quantitative review that can compare results across studies is greatly needed.

Prior articles have narratively summarized age differences in TS [18; 24] and CPM [18]; however, a significant amount of studies have since been published on this topic. Furthermore and to the best of our knowledge, no quantitative reviews examining age differences in TS and CPM have been published in the literature. Meta-analytic methods offer a means to determine the magnitude of age differences across younger, middle-aged, and older adults, as well as the magnitude of pain inhibition or pain facilitation observed on these pain modulatory tests within groups. Therefore, to extend and update the work in the previous reviews, the purpose of this study was to use meta-analytic methodology to examine age differences in CPM and TS among healthy younger, middle-aged, and older adults.

Methods

Search Strategy

Temporal summation and CPM studies that compared these measures between younger, middle-aged, and older adults were located on computer based searches conducted

on PubMED, Psych Info, Embase, CINAHL, and Academic Search Premier databases from 1900 to June 2019. The key words included in the search were chosen from two groups of words: Group 1 ('temporal summation', 'wind-up pain', 'conditioned pain modulation', 'diffuse noxious inhibitory control', or 'diffuse noxious inhibitory controls') *and* Group 2 ('aging', 'older adults' or 'elderly'). For each database, the search included one key word from Group 1 in combination with one key word from Group 2, so that all possible combinations of key words from the two groups were searched. These searches were extended by examining reference sections from published articles identified from the databases and review articles. We believe that these studies represent a comprehensive selection of empirical studies. Only published research was included in the analysis, which may have biased the results as non-significant results are less likely to be published than those with significant findings. When studies did not provide adequate statistical information for the calculation of effect sizes, means and standard deviations were estimated from figures and authors were contacted via electronic mail.

Eligibility Criteria

To be included all studies had to meet the following criteria: 1) pain induction protocol was standardized, 2) study included two of the following age groups: a healthy younger group, middle-aged group, or healthy older adult group, 3) age groups included individuals that did not have any chronic/acute pain disease, 4) data for effect sizes could be obtained. Due to the heterogeneity in studies defining younger, middle-aged, and older adult age groups, we were not able to use defined age ranges for each category, as this would have excluded many of the studies. Additionally, studies were included in the CPM analysis if they met the following criteria: 1) noxious pain stimuli for both test and conditioning stimulus were used in CPM protocol, 2) the sequence of the CPM protocol was the test stimulus before and during/after conditioning stimulus, 3) subjective pain assessment (e.g., VAS or NRS),

pain threshold assessment or nociceptive flexion reflex was one of the outcomes or measurements of the CPM effect. Studies were included in the TS analysis if they met the following criteria: 1) subjective pain assessment (e.g., VAS or NRS) or nociceptive flexion reflex was used during the TS protocol, and 2) repeated pain stimulus administered at a constant intensity. Studies that were review articles or animal studies were not included.

Screening and selection of records

The literature search located a total of 1655 records and 958 non-duplicated records. These records were first screened via title and abstracts independently by two researchers (J.H. and K.M.N.), separately. If any disagreement existed, the article was included in the full-text review. After initial screening, 45 full text articles were assessed for eligibility within our group. Any disagreement was settled by discussion and consensus of the group. Figure 1 provides an overview of the study screening and selection process for TS and CPM, separately. A total of 11 studies met criteria to be included in the CPM analysis, consisting of 848 participants (377 younger adults, 184 middle-aged adults, 287 older adults) and 38 effects. Eleven studies met criteria to be included in the TS analysis, consisting of 873 participants (484 younger adults, 108 middle-age adults, 331 older adults) and 99 effects.

Data extraction and risk of bias assessment

Two researchers (J.H. and K.M.N.) extracted data from the eligible articles on the following predefined parameters: 1) bibliographic details, 2) demographics of sample, 3) CPM or TS protocol characteristics, 4) primary outcome measures, 5) data to calculate effect sizes. Two researchers (K.M.N. and K.E.N.) also assessed the risk of bias of selected studies using the criteria suggested by Lewis and colleagues in risk assessment for CPM comparison studies [21]. This risk of bias assessment has been utilized in other meta-analyses examining group differences in CPM and TS [25; 32]. The original scale was used for studies

comparing cases (e.g., chronic pain group) and controls; however, we adapted the scale for comparability of age groups. This scale assesses the risk of bias/quality of studies in meta-analyses by assessing four categories. The first category assesses blinding of outcome assessors to participant group with the following criteria: explicitly stated = 0, implied but not explicit = 1, assessment not blinded or not stated = 2. The second category assesses whether the age groups are representative of the population based on inclusion criteria and recruitment procedures: age-group inclusion criteria and recruitment procedure specified = 0, either age-group inclusion criteria or recruitment procedure not used or not specified = 1, age-group inclusion criteria and recruitment procedure not used or not specified = 2. The third category assesses comparability of older and younger age groups. This scale is typically based on age and sex; however, for this review assessment was based on sex and race comparability: < 10% difference between groups in male/female participants numbers and in racial composition = 0, Either > 10% difference between groups in male/female participants numbers or in racial composition (or data not reported) = 1, > 10% difference between groups in male/female participants numbers and in racial composition (or data not reported) = 2. The final criteria was based on controlled risk of known confounders including controlling for caffeine intake and medications prior to testing, presence of acute and chronic pain conditions, phase of menstrual cycle for females, and presence of cognitive impairment (e.g., assessed by Mini Mental Status Examination). The scoring of known confounders included the following: ≥ 4 of the named confounders controlled = 0; 3 of the named confounders controlled = 1, 2 or fewer of the named confounders controlled = 2. The total score for a study ranges from 0 to 8, with higher scores representing higher risk of bias. Discrepant scores between researchers were resolved by consulting with the third author (J.H.) and discussion within the group.

Statistical Analysis

The effect sizes (ES) for TS and CPM for each study were calculated using Cohen's *d*, but in two potential ways which are summarized in Figure 2. First, for those studies providing a TS or CPM score for each age group [6; 9; 10; 16; 17; 20; 26; 27; 29; 33; 38; 39], Cohen's *d* was defined as the mean for the younger or middle-aged group minus the mean for the older group, divided by the pooled within group standard deviation ($\underline{d}$=[$X_{younger}$ − X_{older}]/pooled standard deviation). Thus, the single effect size represented the magnitude of between-group age differences, with a higher ES indicating greater TS (pain facilitation) for the older group or greater CPM (greater inhibition) for the younger group. If group means for TS and CPM were not reported [1; 7; 10; 19; 22; 24; 28; 39; 44], then effect sizes were calculated for the magnitude of the CPM or TS effect within each age group. For TS, *d* was defined as the mean for max or final stimulus pain rating minus mean for the first or single stimuli pain rating, divided by the pooled within group standard deviation ($\underline{d}$=[$X_{final/max\ stimulus}$ − $X_{first\ stimulus}$]/pooled standard deviation). A higher ES represented a greater magnitude of TS. For CPM, *d* was defined as the mean for the post conditioning test stimulus minus the mean for the pre-conditioning test stimulus, divided by the pooled within group standard deviation ($\underline{d}$=[$X_{post\ test\ stimulus}$ − $X_{pre\ test\ stimulus}$]/pooled standard deviation). A higher ES represented a greater magnitude of pain inhibition on the CPM test. The within-subject effect sizes were adjusted as recommended by Portney and Watkins [34]. Effect sizes were interpreted as small (0.20), medium (0.50), and large (0.80) [3].The mean effect sizes of $\underline{d}$ for TS and CPM were calculated separately for between age-group effects and within-age group effects using the pooled effect sizes. Due to the variation in sample sizes, it has been argued that not all studies in meta-analyses should be given equal weight. Hedges, noting the bias in estimates of $\underline{d}$ when weighting for sample size, developed a weighted estimator of effect size (*d*) which is asymptotically efficient and appropriate for group sizes greater than 10 [12; 13]:

$d = \Sigma wd/\Sigma w$ where $w=2N/8 + d^2$

In order to quantify the heterogeneity among studies, we also calculated the I^2 index [15; 31]. The I^2 index is calculated by dividing the difference between the result of the *Q* test and its degrees of freedom (*k* - 1) by the *Q* value itself and multiplied by 100. The *Q* value is computed by summing the squared deviations of each study's effect estimate from the overall effect estimate, weighting the contribution of each study by its inverse variance. The I^2 index is interpreted as the percentage of total variability in a group of effect sizes caused by true heterogeneity (i.e., between studies variability). Higgins and Thompson suggested that I^2 values of 25%, 50%, and 75% indicate low, medium, and high heterogeneity, respectively [15]. A value of "0" would mean that all variability in the effect sizes is due to sampling error within studies, rather than true heterogeneity between studies.

In sum, we report the mean of the raw effect size $\underline{d}$, standard deviation and 95% confidence interval of $\underline{d}$, weighted mean effect size (d), and I^2. When feasible, effect sizes were also grouped by different protocol procedures (i.e., inter-stimulus intervals (ISI's), pain induction method, concurrent or nonconcurrent CPM protocol).

RESULTS

As mentioned in the Methods, the studies were first divided according to TS or CPM. Within each test of pain modulation, the studies were divided into between-age group effects and within-age group effects. As previously mentioned, the age ranges for age groups varied widely between studies. Generally, younger adult groups included age ranges that fell between 18 and 45, middle-age groups included age ranges that fell between 40 and 65, and older adult groups included age ranges ranging from 55 and older.

Temporal Summation of Pain Results

Between Age-group Differences in TS

Table 1 presents the characteristics and effect sizes for the seven TS studies with effect sizes calculated between age groups [6; 10; 26; 27; 29; 33; 38]. In these studies, we

were able to examine age differences in TS by calculating between-age group effect sizes that represented which group had a greater magnitude of TS (378 younger adults, 108 middle-aged adults, 204 older adults, 19 effects). These studies included younger vs. older adult comparisons (5 studies: 276 younger adults, 180 older adults, 13 effects) [6; 26; 27; 29; 38], younger vs. middle-age comparisons (2 studies: 190 younger adults, 82 middle-aged adults, 5 effects) [10; 38] and middle-age vs. older adult comparisons (1 study: 26 middle-aged adults, 24 older adults, 1 effect) [33]. As demonstrated in Table 1, the TS protocol used by studies varied widely based on test stimuli, body location, and inter-stimulus-intervals (ISI). Five studies used heat stimuli as the method of pain induction (14 effects) [6; 26; 27; 29; 38], two studies used pressure cuff stimuli (3 effects) [10; 33], and one study used cold pain stimuli (2 effects) [27]. Studies also differed based on ISI. Two studies included TS protocols with ISI's at 3.5 seconds or greater (4 effects) [26; 38] and all studies included TS protocols with ISI's at 3-seconds or less. Finally, the studies also differed on the method used to calculate the TS score. Two studies calculated TS by comparing the first stimulus pain rating to the maximum pain rating following stimuli [6; 29], three studies compared the first stimulus pain rating to the 10^{th} stimulus pain rating [26; 27; 38], and two studies calculated a ratio of the mean intensity rating for stimuli 1-4 and stimuli 8-10 [27; 33].

The summary results (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, weighted mean effect size (d), and I^2 averaged within younger vs. older adult comparisons and younger vs. middle-aged adult comparisons) are shown in Table 2. When averaged across pain stimuli and inter-stimulus-intervals (ISI's), the effect size for age differences between younger and older adults in TS was positive and moderate at 0.46 and when adjusted for sample size and bias, 0.47. Similarly, the average effect size for the studies comparing younger to middle-aged adults was 0.43. This means that overall older adults and middle-aged adults exhibit greater TS compared to younger adults, and that this difference is small to

moderate in magnitude. However, the one study comparing middle-aged adults to older adults revealed only a small magnitude of difference, with older adults demonstrating greater TS.

When evaluating effect sizes in the younger vs. older adult comparison studies by pain induction method, age differences were moderate during heat TS and small in cold TS. Additionally, we subdivided effect sizes in younger vs. older studies based on ISI of the TS test because prior work suggests that older adults may exhibit enhanced summation of pain at ISI's of greater than 3-seconds [19; 36]. Age differences in TS were enhanced when the ISI's were above 3-seconds (IPI $\leq$ 3 sec, d= 0.33; IPI > 3 sec, d = 0.85).

Magnitude of TS within Younger, Middle-aged, and Older Adult groups

Table 3 presents the characteristics and effect sizes for the four TS studies with effect sizes calculated for the magnitude of TS within each age group (127 younger adults, 107 older adults, 80 effects) [1; 7; 19; 24]. One study provided data on TS separated by age group and race; thus, effect sizes are presented for non-Hispanic whites (NHW) and African Americans (AA) separately for this study [1]. As shown in Table 3, generally, all groups showed some degree of pain facilitation during TS protocols (represented by positive effect size), except when electrical stimulation applied at a low frequency was the induction stimulus and the nociceptive reflex was the outcome measure. Two studies used heat stimuli as the method of pain induction (28 effects) [1; 19], two studies used electrical stimuli (40 effects) [7; 24], one study used punctate stimuli (8 effects) [1] and one study used pressure stimuli (4 effects) [19]. Three studies included TS protocols with ISI's at 3-seconds or greater (24 effects) [7; 19; 24] and all studies included TS protocols with ISI's less than 3-seconds (56 effects). Finally, differences again existed in the way studies calculated the TS score. Three studies calculated the TS score by comparing the single stimulus rating to the 5^{th} stimulus rating [7; 19; 24], while one study compared the first stimulus rating to the max pain

rating [1], and the study using punctate stimuli compared a single contact rating to the most painful of 10 contacts [1].

The summary results (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, weighted mean effect size (d), and I^2 averaged within younger and older adult groups) are shown in Table 4. Both age groups demonstrated a moderate effect size for the magnitude of temporal summation, with older adults being slightly higher (0.51 vs. 0.66). In partitioning effect sizes by pain induction stimulus, small effect sizes were seen for heat stimuli with little difference between groups (younger d=0.25, older d= 0.31). Large effects sizes were seen for both age groups with electrical and punctate TS, with older adults showing a slightly larger magnitude of TS. When pressure stimuli were used, younger adults exhibited a moderate magnitude of TS while older adults showed a large magnitude. When examining TS effect sizes based on ISI, effect sizes were moderate to large and quite similar between younger and older adults when TS was administered with an ISI below 3-seconds. When the ISI was above 3-seconds, younger adults only demonstrated a small magnitude of TS and older adults showed a moderate effect size.

Conditioned Pain Modulation Results

Between Age-group Differences in CPM

Table 5 presents the characteristics and the effect sizes for the seven studies with effect sizes calculated between age groups for CPM [6; 9; 16; 17; 20; 33; 39]. In these studies, we were able to examine age differences in CPM by calculating between-age group effect sizes that represented which group had a greater magnitude in CPM (232 younger adults, 133 middle-aged adults, 170 older adults, 16 effects). These studies included younger vs. older adult comparisons (6 studies: 232 younger adults, 146 older adults, 8 effects) [6; 9;

16; 17; 20; 39], middle-aged vs. older adult comparisons (4 studies: 133 middle-aged adults, 89 older adults, 6 effects) [9; 16; 17; 33], and younger vs. middle-aged adult comparisons (1 study: 106 younger adults, 70 middle-aged adults, 2 effects) [16].

As demonstrated in Table 5, some variation existed between CPM protocols. Two studies used suprathreshold pressure pain as the test stimulus [21; 33], one study used mechanical TS [16], and all other studies used some type of heat stimuli [6; 9; 17; 39]. However, the type of heat stimulus varied widely between studies and included heat pain thresholds [17], prolonged suprathreshold heat pain [9; 39], and heat temporal summation [6]. The test stimulus was mostly applied to the upper limb (palm, finger, or forearm) [6; 9; 16; 20; 39], while two studies applied it to lower limbs [17; 33], and one study applied the test stimulus intraorally [16]. All but two studies used cold water immersion as the conditioning stimulus applied to either the contralateral foot [9; 20; 39] or hand [6; 17]. One study used hot water immersion [16] and the other study used pressure cuff stimulation as the conditioning stimulus [33]. In terms of the overall CPM protocol, one study used a non-concurrent protocol in which the test stimulus was delivered before and after the conditioning stimulus [9], while all other studies used a concurrent protocol (test stimulus delivered during conditioning stimulus).

The summary results for between age-group differences in CPM (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, weighted mean effect size (d), and I^2 averaged within younger vs. older adult comparisons, younger vs. middle-aged adult comparisons, and middle-aged vs. older adults comparisons) are shown in Table 6. The magnitude of difference between younger and older adults in CPM was large, with younger adults demonstrating greater pain inhibition during CPM protocols. Interestingly, we found small effects in the younger vs. middle-aged adult comparisons and older vs. middle-aged adult CPM comparisons, with the younger group demonstrating greater pain inhibition in both scenarios. Averaging the effect

sizes for the concurrent and non-concurrent CPM protocols separately did not change the results.

Magnitude of CPM within Younger, Middle-aged, and Older Adult groups

Table 7 presents the characteristics and effect sizes for the five CPM studies with effect sizes calculated for the magnitude of CPM within each age group (5 studies: 187 younger adults, 34 middle-aged adults, 117 older adults, 22 effects) [10; 22; 28; 39; 44]. Four studies used cold water immersion of either the foot [28; 39] or hand [10; 44] and 1 study used cold plate contact as the conditioning stimulus [22]. All studies used different test stimuli in the CPM protocol. Two studies used prolonged heat pain applied to the left palm as the test stimulus [28; 39], one study used heat pain threshold on the hand [22], one study used pressure cuff algometry of the non-dominant leg [10], and one study used electrical and heat pain thresholds applied to the hand [44]. One study used a concurrent CPM protocol [39] and five studies used a non-concurrent CPM protocol [10; 22; 28; 39; 44].

The summary results for the magnitude of CPM within the different age groups (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, weighted mean effect size (d), and I^2 averaged within younger and older adult groups) are shown in Table 8. The results indicated that the magnitude of pain inhibition on the CPM test was large for younger adults and small for older adults. When examining the effects sizes based on concurrent vs. non-concurrent protocols, older adults showed a small to moderate magnitude of pain inhibition during non-concurrent protocols but a small magnitude of pain facilitation during concurrent CPM protocols. Younger adults demonstrated a large magnitude of pain inhibition regardless of CPM protocol, with non-concurrent protocols eliciting a larger effect. Un-expectantly, the one study evaluating younger vs. middle-aged adults found a small and moderate magnitude of pain inhibition in younger and middle-aged adults, respectively.

Risk of Bias Results

The risk of bias results for all selected studies are presented in Table 9. The bias scores ranged from 3 to 7, with most studies scoring a 5 (37%), followed by 3 (26%) and 4 (26%). The average risk bias score was 4.37 ± 1.09. We found that the most common bias risks included poor blinding of outcome assessments, ensuring comparability of race between groups, and controlling for menstrual cycle phase during assessment of females. Indeed, no studies attempted to blind the outcome assessments or controlled for menstrual cycle. Majority of studies did not report the racial composition of the sample. Most studies were low risk for cases representative of the population (84.2%). Additionally, most studies ensured comparability between groups on male/female ratio (68.4%), and controlled for medications prior to assessment (100%) and presence of pain conditions (100%).

DISCUSSION

To the best of our knowledge, this is the first study to systematically review and quantify the age differences in pain facilitation on the TS test and pain inhibition on the CPM test with meta-analytic techniques. Effect sizes were derived from 19 studies that compared healthy younger, middle-aged, and older adults that were free of chronic pain on measures of TS and CPM. Overall, the results suggested that older adults exhibit maladaptive endogenous pain facilitation and inhibition compared to younger adults, with these deficiencies potentially starting in middle-age.

Age Group Differences in TS

The overall unbiased between-age group differences for younger vs. older adults in TS was moderate, with the magnitude of the effect varying substantially (-0.20 to 1.10). The effect sizes also revealed small to moderate differences between younger and middle-aged adults. Within age groups, younger adults demonstrated a moderate magnitude of TS, while older adults demonstrated a moderate to large magnitude of TS. However, the magnitude of

effect varied greatly within both age groups (younger adults: -0.10 to 2.48; older adults: -0.55 to 2.14). Several factors likely contributed to the mixed results and broad range of effect sizes found in the selected studies, which is discussed in detail in the paragraphs that follow.

One potential factor influencing age-related differences in TS of pain is the stimulus modality used to induce TS, which theoretically could activate different primary nociceptive afferents. For example, mechanical TS compared to heat TS likely involves greater activation of A-fibers due to the "pricking" sensation elicited during mechanical TS that is not present during heat TS [48]. Furthermore, prior research suggests a differential change in A-fiber vs. C-fiber mediated pain perception with age, such that older adults exhibit a greater decline in the function of A delta fibers [2]. Thus, TS protocols using different stimulus modalities could theoretically be differentially impacted by age. Analysis of within-group effect sizes showed that the magnitude of summation varied among the different stimulus induction methods, with older adults exhibiting a slightly greater magnitude of TS compared to younger adults regardless of the type of stimuli (heat, electric, punctate, pressure). Notably, the two studies inducing TS with electrical stimuli found no age differences when TS was assessed with the RIII-reflex. The RIII-reflex has greater reliance on spinal nociceptive transmission and activation of A delta fibers, suggesting that facilitation of spinal nociceptive transmission may not be impacted by aging [7; 24]. Between age-group comparisons revealed on average a moderate difference during heat TS, with effect sizes ranging from small to large (0.15 to 1.10). However, when TS was induced by cold stimuli, the average between-group effect size was small. Several studies directly compared age-related differences in TS using more than one stimulus modality. For example, Lautenbacher et al. found age differences in heat TS but not in pressure cuff TS [19]. In contrast, Bulls and colleagues revealed age differences in mechanical TS at the knee and hand, but no age-related differences in heat TS [1]. Notably, the age differences in mechanical TS were somewhat driven by older African American

adults (discussed further below), and the older group included middle-aged and older adults (45-82 years old). Another methodological difference between the studies is that Bulls used heat TS trials at 44, 46, and 48^{o}C, whereas Lautenbacher used individualized temperatures. Overall, the effect size data suggests that age-differences in TS do not substantially differ based on pain-induction method. However, given the small number of effects for some pain induction methods (i.e., punctate, pressure, cold) and the lack of studies comparing multiple TS modalities, more research is needed to confirm whether the source of nociceptive input is a potential important factor influencing age-related differences in TS.

Researchers have hypothesized that age differences in TS are enhanced when TS protocols are administered with longer intervals between stimuli because older adults may have a slower decay of spinal excitability between stimuli. However, the evidence on whether age-related differences in TS are a function of ISI is mixed. Based on the between-group effect size data, age group differences in TS appeared to be magnified with greater ISI's. Several studies directly compared TS with different ISI's. Farrell and Gibson administered electrical TS at five different frequencies ranging from 0.2 Hz to 2 Hz in younger and older adults [7]. When evaluating pain ratings following the electrical pulses, the younger adults only showed pain facilitation during frequencies of 0.33 Hz and higher. However, the older adults demonstrated significant pain facilitation during TS administered at all frequencies. Using a similar experimental paradigm, Marouf and colleagues revealed no age differences in electrical TS (RIII-reflex amplitude or pain ratings) across all stimulus frequencies (0.17 Hz to 2.0 Hz) [24]. Similar to Marouf et al., Lautenbacher and colleagues did not report an age by stimulus frequency interaction when applying heat and pressure TS (ISI 2.4-sec vs. 6.4-sec) [19]. Most recently, Riley et al revealed that middle-aged and older adults exhibited greater TS of heat pain at longer ISI's compared to younger adults [38]. Given the conflicting

evidence to date, no conclusions can be drawn regarding whether age-differences in TS are a function of ISI.

Other potential factors influencing age-related differences in TS include the site of stimulation and the dimension of pain being measured. Haskins et al found that older adults show slow temporal summation of heat pain at the forearm but not the leg (data could not be obtained, and thus not included in this meta-analysis) [11]. The authors' hypothesized that the lack of TS at the leg could be due to age-related axonpathies at distal body sites. In regards to the importance of which dimension of pain is being assessed during TS protocols, Naugle and colleagues conducted two studies evaluating the intensity and spatial perception of the noxious stimuli during TS in younger and older adults [26; 27]. Both studies demonstrated no significant age-related differences in the TS of pain intensity during thermal stimulation, although the results trended in the hypothesized direction. However, the studies revealed greater summation of the size of the painful area in older compared to younger adults, with older females driving the age differences in heat TS (but not cold TS) [27]. These results suggest that age-related differences in pain facilitation on the TS test may be reflected in a greater extent by amplification of spatial rather than amplitude properties of the pain experience. However, more research is needed to confirm this hypothesis.

A weakness of the TS and aging studies is the minimal investigation on potential race by age interactions, given that many laboratory-based pain studies suggest greater experimental pain sensitivity in ethnic minorities. Bulls et al attempted to address this limitation by assessing heat and mechanical TS in two ethnic groups [African Americans (AA), non-Hispanic white (NHW)] and two pain-free age groups (younger and middle-age adults, older adults) [1]. The authors' revealed a race by age interaction for punctate TS at the forearm, which was primarily driven by older AA's demonstrating a greater magnitude of punctate TS compared to all other groups. Similar interaction effects were also evident for

heat TS, but with a lesser magnitude and consistency. While more research is needed to fully understand the effects of minority aging on central pain processing, the current research suggests that older African American adults may be more susceptible to enhanced endogenous pain facilitation.

In sum, older and middle-aged adults compared to younger adults appear to exhibit enhanced TS of pain among a variety of pain induction techniques. The age-related differences appear to start in middle age and be strongest when TS protocols are administered at greater ISI's and measure the spatial properties of the pain experience. However, more studies are needed to verify when TS starts to become amplified across the age span. Some studies also show the potential for race by age and sex by age interactions, with ethnic minorities and women more often showing enhanced pain facilitation in older age. Due to the small number of studies and effects, conclusions regarding the effects of different TS protocol parameters or interactions of these parameters on age differences remain tenable. It is likely that multiple physiological mechanisms underlie enhanced TS of pain in older adults, including age-related decrements in the efficacy of central nervous system pain-regulatory systems and age related changes in the peripheral nervous system (e.g., decline in function of specific fibers [42]). These age-related deficiencies may or may not be involved during a specific TS protocol, depending on the methods used, causing a complex relationship between TS of pain and aging.

Age group differences in CPM

The effect size data suggests a large magnitude of difference in CPM between older and younger adults, with younger adults exhibiting greater pain inhibition. When examining the magnitude of pain inhibition during CPM, younger adults exhibit a large effect while older adults demonstrate a small effect. The evidence also indicates that the decline in pain

inhibitory capacity may begin in middle age. Two studies examined CPM across the adult lifespan revealing a decline in pain inhibition in middle-age that continues to deteriorate thereafter [9; 17]. Supporting this notion, our between-group effect size data revealed a trivial between-age group difference in CPM between middle-aged and older adults (*d*= -0.02).

One potential factor influencing the magnitude of CPM in older adults is the use of concurrent vs. nonconcurrent CPM protocols. Two studies investigated age differences in CPM using both types of protocols in the same study [9; 39]. Riley and colleagues revealed that pain facilitatory responses during CPM in older adults are more likely to emerge with concurrent vs. nonconcurrent stimulation of the conditioning and test stimuli [39]. Our within-group effect sizes supported this notion, with older adults demonstrating a small magnitude of pain facilitation during CPM concurrent protocols. However, older adults show a moderate magnitude of pain inhibition when the test stimulus is presented before and after the conditioning stimulus (non-concurrent protocols). Riley et al. suggested that older adults may be less able to process multiple noxious stimuli simultaneously as in concurrent protocols, possibly due to cognitive overload. It should be noted that Grashorn and colleagues found very low levels of pain inhibition in older and middle-aged adults during the non-current protocol and in older adults during the concurrent protocol, but pain facilitation for middle-age adults during the concurrent protocol [9]. Given the small number of studies addressing this issue, future research is needed to confirm whether age-related pain facilitation during CPM is dependent on the temporal presentation of the test and conditioning stimuli.

Minimal research exists that evaluates sex by age and race by age interactions on CPM. Only one study to our knowledge investigated whether an age by race interaction exists on CPM. Comparing middle-aged and older adults, Riley et al revealed no race and age

differences in CPM [37]. Indeed, neither older or middle-aged African Americans and non-Hispanic Whites exhibited significant pain inhibition on the CPM test. However, this study was not included in the meta-analysis because the sample included participants with mild osteoarthritis. The one study examining sex and age differences in CPM found no sex differences across the age span [9]. However, the number of males and females within each age group was relatively small to test for interactions.

Limitations

Some additional limitations exist within this systematic review. First, studies included in this review used varying definitions of older, younger, and middle age groups and some lumped two age groups into one. Additionally, the majority of studies evaluated age *group* comparisons in pain modulation, even though age is a continuous variable. The few studies examining age as a continuous variable supported the notion that endogenous pain modulation declines with age. Indeed, the studies revealed significant correlations between aging and punctate TS (r=.387, .483) [1] and aging and CPM (absolute r=.41, .398) [9; 17]. Second, while trends could be identified, the impact of various protocol parameters and interaction of these parameters on age-related differences in CPM and TS could not be systematically determined with the amount of data available. Third, accumulating research suggests that individual differences in CPM and TS within the healthy older adult cohort may exist due to variation in psychological and behavioral variables. For example, Naugle et al. revealed that physically active older adults exhibit more efficacious CPM and TS compared to healthy sedentary older adults [30]. Furthermore, Marouf and colleagues demonstrated that reduced CPM is associated with reduced cognitive inhibition in younger and older adults [23]. A recent meta-analysis also revealed that several psychological factors (i.e., depression, anxiety, pain catastrophizing) are associated with modality-specific CPM responses in healthy individuals. Thus, age-related differences in central pain processing are likely

influenced by individual patient factors, which could not all be addressed in this review. Importantly, future research needs to continue to evaluate potential factors/confounders (e.g., physical activity, psychological factors) that may alter the aging and pain modulation relationship. Fourth, all studies included in this review had some level of risk of bias. In particular, studies did not mention blinding the assessment of TS or CPM and rarely considered or reported on the comparability of the racial composition of groups. Moreover, most studies did not control for all known potential confounders that could influence the testing of TS and CPM. Finally, in regards to the between-age group effects in TS, four out of the seven studies (15/19 effects) came from the same lab.

Conclusions

Despite the variability in stimulation parameters and methodology between studies, data from this study provided strong quantitative evidence of a general age-related increase in TS and decline in CPM, suggesting dysfunctional endogenous pain mechanisms in healthy older compared to healthy younger adults. Future studies are needed to determine whether these age differences in endogenous pain modulation apply to adults with chronic pain. For example, several studies examining age differences in TS and CPM in pain patients reported no age effects on CPM in patients with mild knee osteoarthritis [37] and a variety of pain conditions [40], as well as no age effects on TS in mild [37] and severe knee osteoarthritis [33]. However, it should be noted that two out of the three studies did not include a younger adult cohort. Along these lines, future investigations are needed to determine whether abnormal pain modulation on the TS and CPM tests predict clinical outcomes with aging. Furthermore, future studies need to determine the behavioral, physiological, and biological mechanisms underlying the decline in endogenous pain modulation with aging. Importantly, all future studies focused on aging and pain modulation should strive for high methodological quality, and in particular overcome the shortcomings in the prior literature such as ensuring

comparability of race between groups and controlling for as many known confounders as possible.

References

[1] Bulls HW, Goodin BR, McNew M, Gossett EW, Bradley LA. Minority Aging and Endogenous Pain Facilitatory Processes. Pain Med 17(6):1037-1048, 2016.

[2] Chakour MC, Gibson SJ, Bradbeer M, Helme RD. The effect of age on A delta- and C-fibre thermal pain perception. Pain 64(1):143-152, 1996.

[3] Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York, NY: Routledge Academic, 1988.

[4] Edwards RR, Fillingim RB. Effects of age on temporal summation and habituation of thermal pain: clinical relevance in healthy older and younger adults. J Pain 2(6):307-317, 2001.

[5] Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 101(1-2):155-165, 2003.

[6] Edwards RR, Ness TJ, Weigent DA, Fillingim RB. Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 106(3):427-437, 2003.

[7] Farrell M, Gibson S. Age interacts with stimulus frequency in the temporal summation of pain. Pain Med 8(6):514-520, 2007.

[8] Gagliese L, Melzack R. Age differences in nociception and pain behaviours in the rat. Neurosci Biobehav Rev 24(8):843-854, 2000;.

[9] Grashorn W, Sprenger C, Forkmann K, Wrobel N, Bingel U. Age-dependent decline of endogenous pain control: exploring the effect of expectation and depression. PLoS One 8(9):e75629, 2013.

[10] Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. Pain 156(11):2193-2202, 2015;.

[11] Harkins SW, Davis MD, Bush FM, Kasberger J. Suppression of first pain and slow temporal summation of second pain in relation to age. J Gerontol A Biol Sci Med Sci 51(5):M260-265, 1996;.

[12] Hedges L. Distribution theory for Glass's estimator of effect size and related estimators. J Educat Stat 6:490-499, 1981.

[13] Hedges L. Estimation of effect size from a series of independent experiments. Psychol Bull 92:490-499, 1982.

[14] Helme RD, Gibson SJ. The epidemiology of pain in elderly people. Clin Geriatr Med 17(3):417-431, 2001.

[15] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539-1558, 2002.

[16] Khan J, Korczeniewska O, Benoliel R, Kalladka M, Eliav E, Nasri-Heir C. Age and gender differences in mechanically induced intraoral temporal summation and conditioned pain modulation in healthy subjects. Oral Surg Oral Med Oral Pathol Oral Radiol 126(2):134-141, 2018.

[17] Lariviere M, Goffaux P, Marchand S, Julien N. Changes in pain perception and descending inhibitory controls start at middle age in healthy adults. Clin J Pain 23(6):506-510, 2007.
[18] Lautenbacher S. Experimental approaches in the study of pain in the elderly. Pain Med 13 Suppl 2:S44-50, 2012.
[19] Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 115(3):410-418, 2005.
[20] Lemley KJ, Hunter SK, Bement MK. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. Med Sci Sports Exerc 47(1):176-184, 2015.
[21] Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 13(10):936-944, 2012.
[22] Lithfous S, Despres O, Pebayle T, Dufour A. Modification of Descending Analgesia in Aging: Critical Role of the Prefrontal Cortex. Clin J Pain 35(1):23-30, 2019.
[23] Marouf R, Caron S, Lussier M, Bherer L, Piche M, Rainville P. Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. Pain 155(3):494-502, 2014.
[24] Marouf R, Piche M, Rainville P. Is temporal summation of pain and spinal nociception altered during normal aging? Pain 2015;156(10):1945-1953.
[25] Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: a systematic review and meta-analysis. Pain 159(8):1441-1455, 2018.
[26] Naugle KM, Cruz-Almeida Y, Fillingim RB, Staud R, Riley JL, 3rd. Novel method for assessing age-related differences in the temporal summation of pain. J Pain Res 9:195-205, 2016.
[27] Naugle KM, Cruz-Almeida Y, Fillingim RB, Staud R, Riley JL, 3rd. Increased spatial dimensions of repetitive heat and cold stimuli in older women. Pain 158(5):973-979, 2017.
[28] Naugle KM, Cruz-Almeida Y, Vierck CJ, Mauderli AP, Riley JL, 3rd. Age-related differences in conditioned pain modulation of sensitizing and desensitizing trends during response dependent stimulation. Behav Brain Res 289:61-68, 2015.
[29] Naugle KM, Naugle KE, Riley JL, 3rd. Reduced Modulation of Pain in Older Adults After Isometric and Aerobic Exercise. J Pain 17(6):719-728, 2016.
[30] Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior predicts endogenous pain modulation in older adults. Pain 2017;158(3):383-390.
[31] Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. BMC Res Notes 5:52, 2012.
[32] O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, Carrillo-de-la-Pena MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. J Pain 19(8):819-836, 2018.
[33] Petersen KK, Arendt-Nielsen L, Finocchietti S, Hirata RP, Simonsen O, Laursen MB, Graven-Nielsen T. Age Interactions on Pain Sensitization in Patients With Severe Knee Osteoarthritis and Controls. Clin J Pain 33(12):1081-1087, 2017.
[34] Portney L, Watkins M. Foundations of clinical research: applications to practice. East Norwalk, CT: Appleton and Lang, 1993.
[35] Price DD. Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol 37(2):371-387, 1972.
[36] Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous systems. J Invest Dermatol 69(1):167-171, 1977.

[37] Riley JL, 3rd, Cruz-Almeida Y, Glover TL, King CD, Goodin BR, Sibille KT, Bartley EJ, Herbert MS, Sotolongo A, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB. Age and race effects on pain sensitivity and modulation among middle-aged and older adults. J Pain 15(3):272-282, 2014.
[38] Riley JL, 3rd, Cruz-Almeida Y, Staud R, Fillingim RB. Effects of manipulating the interstimulus interval on heat-evoked temporal summation of second pain across the age span. Pain 160(1):95-101, 2019.
[39] Riley JL, 3rd, King CD, Wong F, Fillingim RB, Mauderli AP. Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. Pain 150(1):153-160, 2010.
[40] Skovbjerg S, Jorgensen T, Arendt-Nielsen L, Ebstrup JF, Carstensen T, Graven-Nielsen T. Conditioned Pain Modulation and Pressure Pain Sensitivity in the Adult Danish General Population: The DanFunD Study. J Pain 18(3):274-284, 2017.
[41] Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Rev Neurother 12(5):577-585, 2012.
[42] Taguchi T, Ota H, Matsuda T, Murase S, Mizumura K. Cutaneous C-fiber nociceptor responses and nociceptive behaviors in aged Sprague-Dawley rats. Pain 151(3):771-782, 2010.
[43] Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 9(10):883-891, 2008.
[44] Washington LL, Gibson SJ, Helme RD. Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain 89(1):89-96, 2000.
[45] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain 19(6):805-806, 2015.
[46] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 138(1):22-28, 2008.
[47] Yezierski RP, King CD, Morgan D, Carter CS, Vierck CJ. Effects of age on thermal sensitivity in the rat. J Gerontol A Biol Sci Med Sci 65(4):353-362, 2010.
[48] Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 122 (Pt 12):2245-2257, 1999.

Table Legends

Figure Legends

Figure 1. Study selection flow chart. ASP=Academic Search Premier; TS=temporal summation; CPM=conditioned pain modulation; ES=effect size.

Figure 2. Flow chart for calculation of effect sizes.

Figure 1.

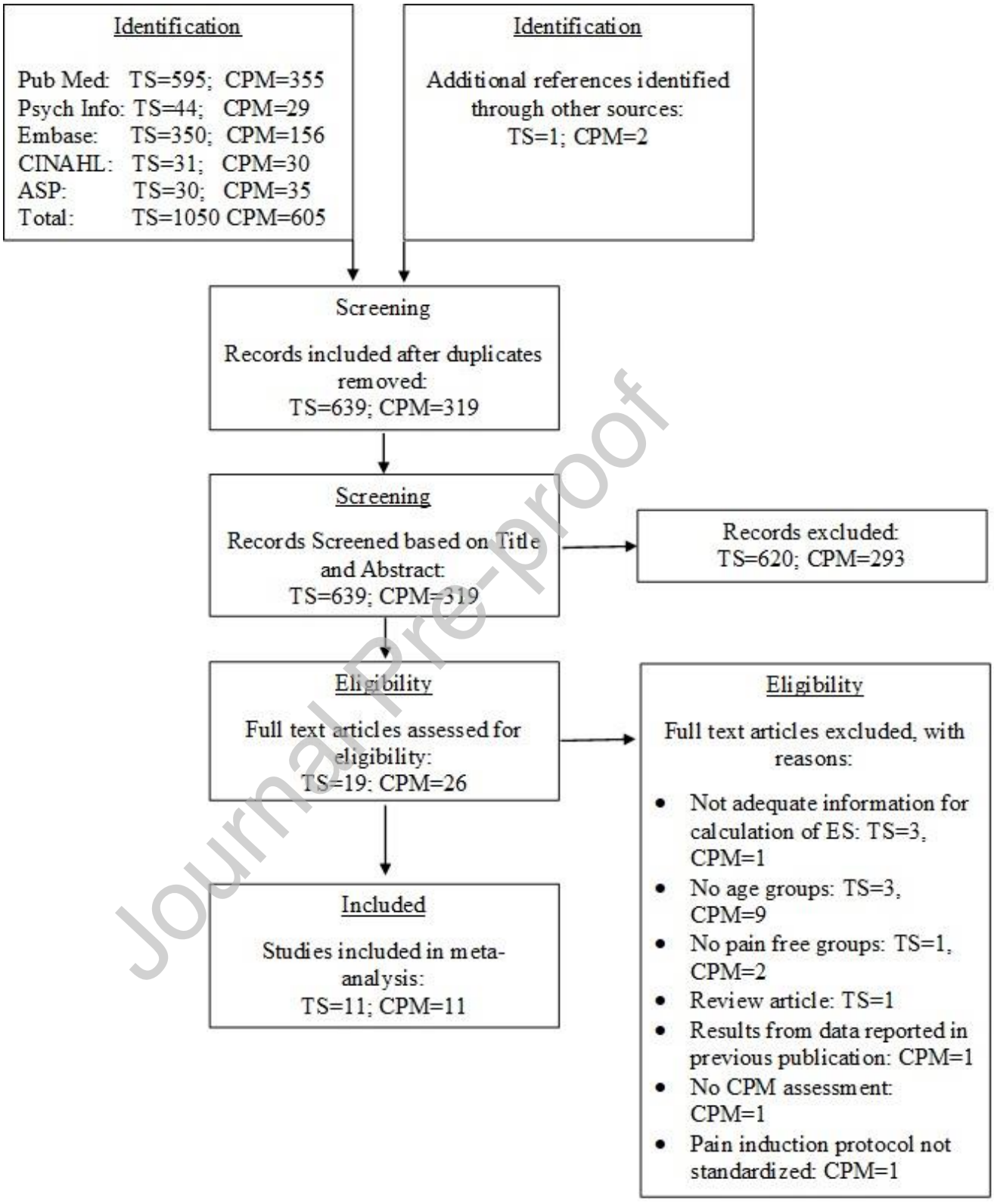

Figure 2.

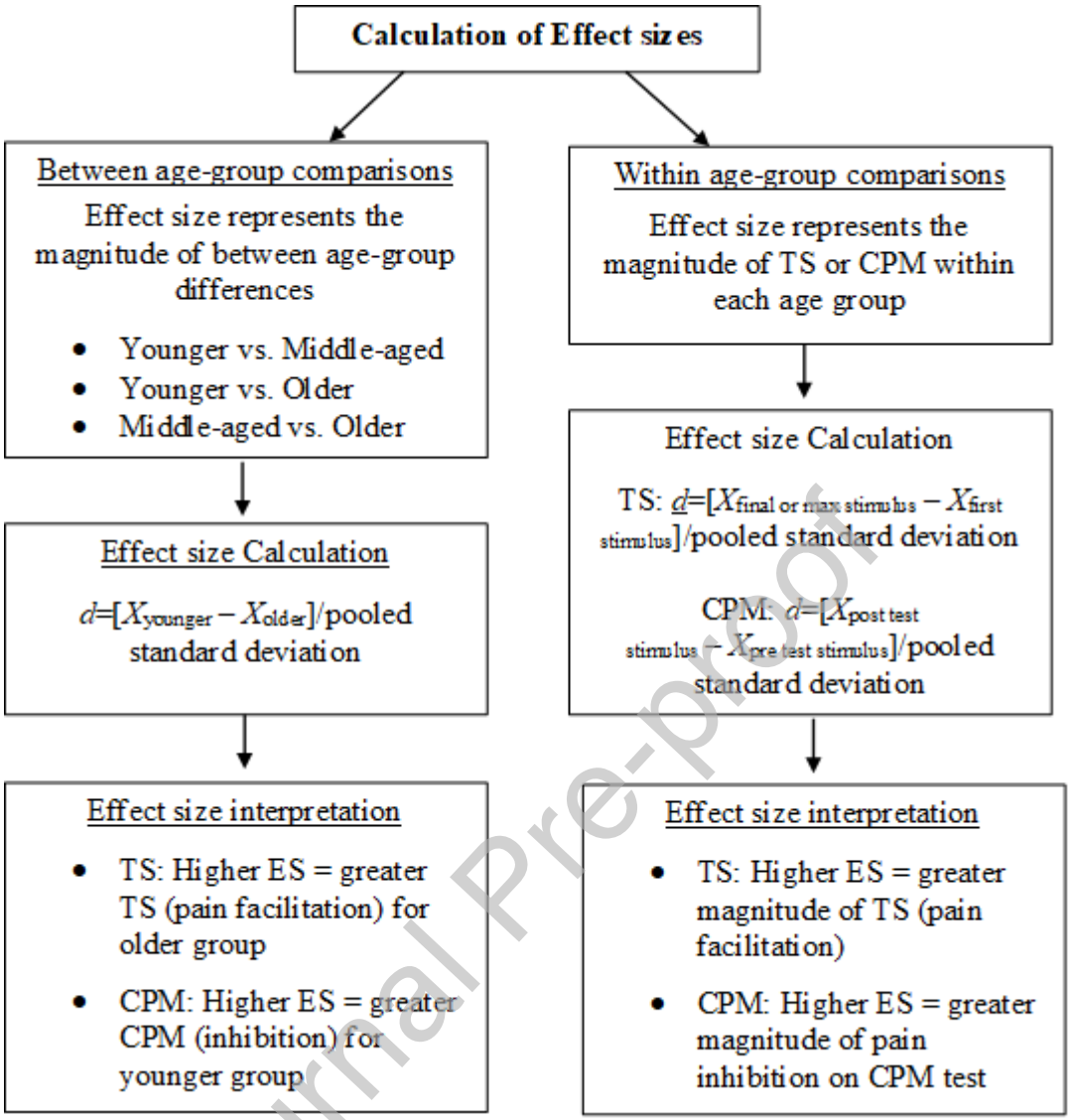

Table 1. Studies examining age differences in TS: Between-age group differences

Author, year	Sample Size (Younger/older or middle/older)	Pain induction stimulus	Pain Induction Location	Number of Stimuli	ISI	Pooled ES
Graven-Nielsen, 2015 [10]	102 Y (18-44 y)/ 34 M (45-65 y)	Pressure cuff algo., intensity ratings	Upper Arm	10	3.0 s	0.38
Graven-Nielsen, 2015	102 Y /34 M	Pressure cuff algo., intensity ratings	Lower Leg	10	3.0 s	0.36
Edwards, 2003 [6]	37 Y (18-25 y)/ 40 O (55-67 y)	Heat, 48.5℃, intensity ratings	Left Hand	10	2.5 s	0.15
Naugle, 2016a [26]	22 Y (18-27 y)/ 20 O (56-77 y)	Heat-ind. intensity ratings	Forearm	10	2.5 s	0.51
Naugle, 2016a	22 Y/20 O	Heat-ind. spatial ratings	Forearm	10	2.5 s	0.58
Naugle, 2016a	22 Y/20 O	Heat-ind. intensity ratings	Forearm	10	3.5 s	0.21
Naugle, 2016a	22 Y/20 O	Heat-ind. spatial ratings	Forearm	10	3.5 s	0.76
Naugle, 2016b [29]	25 Y (19-30 y)/ 18 O (55-74 y)	Heat-ind. intensity ratings	Forearm	10	2.5 s	0.24
Naugle, 2017 [27]	104 Y&M (18-59 y)/ 40 O (60-77 y)	Heat-ind. intensity ratings	Forearm	10	2.5 s	0.34
Naugle, 2017	104 Y/40 O	Heat-ind. spatial ratings	Forearm	10	2.5 s	0.47
Naugle, 2017	104 Y/40 O	Cold-ind. intensity ratings	Forearm	10	2.5 s	-0.20
Naugle, 2017	104 Y/40 O	Cold-ind. spatial ratings	Forearm	10	2.5 s	0.49
Riley, 2019 [38]	88 Y (18-39 y)/ 48 M (40-59 y)	Heat-ind. Intensity ratings	Forearm	10	2.5 s	0.45
Riley, 2019	88 Y/48 M	Heat-ind. Intensity ratings	Forearm	10	3.5 s	0.44
Riley, 2019	88 Y/48 M	Heat-ind. Intensity ratings	Forearm	10	4.5 s	0.54
Riley, 2019	88 Y (18-39 y)/ 62 O (60-80 y)	Heat-ind. Intensity ratings	Forearm	10	2.5 s	0.52
Riley, 2019	88 Y/62 O	Heat-ind. Intensity ratings	Forearm	10	3.5 s	0.85
Riley, 2019	88 Y/62 O	Heat-ind. Intensity ratings	Forearm	10	4.5 s	1.10
Petersen, 2017 [33]	26 M (53-65 y)/ 24 O (65-79 y)	Pressure cuff algo., intensity ratings	Lower Leg	10	1.0 s	0.25

Note. A higher ES indicates greater TS (pain facilitation) for the older group. **ISI=inter-stimulus-interval; y=years old; algo=algometry; ind.=individualized; s=seconds

.**Table 2. Summary of results for age differences in TS between older and younger adults**

TS: Between Group	# of Effects	Mean ES ± SD (95% CI's)	Unbiased ES	I^2
Younger vs. Older adults				
All	13	0.46 ± 0.33 (0.26, 0.66)	0.47	65.7%
Pain Induction Method				
Heat TS	11	0.52 ± 0.29 (0.32, 0.72)	0.57	49.1%
Cold TS	2	0.15 ± 0.49 (-4.23, 4.52)	0.14	85.3%
ISI				
> 3-sec IPI	4	0.73 ± 0.37 (0.13, 1.33)	0.85	52.6%
≤ 3-sec IPI	9	0.34 ± 0.25 (0.15, 0.54)	0.33	34.9%
Younger vs. Middle-age adults				
All	5	0.43 ± 0.07 (0.24, 0.50)	0.43	0.0%
Middle-age vs. Older adults				
All	1	0.25 ± 0.00 (NA)	NA	NA

Note. A higher ES indicates greater TS (pain facilitation) for the older group. The unbiased ES are weighted by sample size. SD=standard deviation; CI=Confidence Interval; ISI=Inter-stimulus-interval.

Table 3. Studies examining age differences in TS: Within age group effects

Author, year	Sample Size (Younger/Older or Middle/Older)	Pain induction stimulus/# of stimuli	Pain induction Location	ISI	Younger ES	Older ES
Lautenbacher, 2005 [19]	20 Y (21-35 y)/ 20 O (63-88 y)	Heat-ind./ 5	Forearm	6.4 s	0.08	0.34
Lautenbacher, 2005	20 Y/20 O	Heat-ind./ 5	Forearm	2.4 s	0.21	0.45
Lautenbacher. 2005	20 Y/20 O	Pressure-ind./ 5	Finger	6.4 s	0.52	0.74
Lautenbacher, 2005	20 Y/ 20 O	Pressure-ind./ 5	Finger	2.4 s	0.31	0.82
Farrell, 2007 [7]	15 Y (18-40 y)/ 15 O (≥ 65 y)	E stim-pulse rating/ 5	R. Lat. Malleolus	0.2 Hz	0.07	0.74
Farrell, 2007	15 Y/15 O	E stim-pulse rating/ 5	R. Lat. Malleolus	0.25 Hz	0.08	1.02
Farrell, 2007	15 Y/15 O	E stim-pulse rating/ 5	R. Lat. Malleolus	0.33 Hz	0.42	1.10
Farrell, 2007	15 Y/15 O	E stim-pulse rating/ 5	R. Lat. Malleolus	1 Hz	0.91	1.63
Farrell, 2007	15 Y/15 O	E stim-pulse rating/ 5	R. Lat. Malleolus	2 Hz	1.32	1.88
Farrell, 2007	15 Y/15 O	E stim-RIII Magnitude/ 5	R. Lat. Malleolus	0.2 Hz	-0.10	-0.55
Farrell, 2007	15 Y/15 O	E stim-RIII Magnitude/ 5	R. Lat. Malleolus	0.25 Hz	-0.10	-0.48
Farrell, 2007	15 Y/15 O	E stim-RIII Magnitude/ 5	R. Lat. Malleolus	0.33 Hz	0.00	-0.40
Farrell, 2007	15 Y/15 O	E stim-RIII Magnitude/ 5	R. Lat. Malleolus	1 Hz	0.78	0.78
Farrell, 2007	15 Y/15 O	E stim-RIII Magnitude/ 5	R. Lat. Malleolus	2 Hz	1.61	1.41
Bulls, 2015* [1]	50 Y (19-35 y)/ 48 M&O (45-82 y)	Punctate/ 10	Knee	1 c/s	0.99 (NHW)	1.12 (NHW)
Bulls, 2015	50 Y/48 M&O	Punctate/ 10	Hand	1 c/s	1.05 (NHW)	1.26 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (44°C)/ 5	Forearm	2.5 s	0.01 (NHW)	0.14 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (46°C)/ 5	Forearm	2.5 s	0.25 (NHW)	0.23 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (48°C)/ 5	Forearm	2.5 s	0.66 (NHW)	0.45 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (44°C)/ 5	Knee	2.5 s	0.17 (NHW)	0.01 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (46°C)/ 5	Knee	2.5 s	0.34 (NHW)	0.44 (NHW)
Bulls, 2015	50 Y/48 M&O	Heat (48°C)/ 5	Knee	2.5 s	0.74 (NHW)	0.55 (NHW)
Bulls, 2015	50 Y/48 M&O	Punctate/ 10	Knee	1 c/s	1.11 (AA)	1.75 (AA)
Bulls, 2015	50 Y/48 M&O	Punctate/ 10	Hand	1 c/s	1.07 (AA)	1.67 (AA)
Bulls, 2015	50 Y/48 M&O	Heat (44°C)/ 5	Forearm	2.5 s	0.14 (AA)	0.24 (AA)
Bulls, 2015	50 Y/48 M&O	Heat (46°C)/ 5	Forearm	2.5 s	0.17 (AA)	0.11 (AA)
Bulls, 2015	50 Y/48 M&O	Heat (48°C)/ 5	Forearm	2.5 s	0.10 (AA)	0.54 (AA)

Bulls, 2015	50 Y/48 M&O	Heat (44℃)/ 5	Knee	2.5 s	0.07 (AA)	0.18 (AA)
Bulls, 2015	50 Y/48 M&O	Heat (46℃)/ 5	Knee	2.5 s	0.21 (AA)	0.23 (AA)
Bulls, 2015	50 Y/48 M&O	Heat (48℃)/ 5	Knee	2.5 s	0.38 (AA)	0.44 (AA)
Marouf, 2015 [24]	21 Y (18-46 y)/ 24 O (56-75 y)	E stim-pulse rating/ 5	R. Sural Nerve	0.17 Hz	0.11	0.85
Marouf, 2015	21 Y/24 O	E stim-pulse rating/ 5	R. Sural Nerve	0.33 Hz	0.30	0.40
Marouf, 2015	21 Y/24 O	E stim-pulse rating/ 5	R. Sural Nerve	0.66 Hz	0.69	0.85
Marouf, 2015	21 Y/24 O	E stim-pulse rating/ 5	R. Sural Nerve	1 Hz	0.72	0.91
Marouf, 2015	21 Y/24 O	E stim-pulse rating/ 5	R. Sural Nerve	2 Hz	0.91	1.05
Marouf, 2015	21 Y/24 O	E stim; RIII Magnitude/ 5	R. Sural Nerve	0.17 Hz	0.71	0.33
Marouf, 2015	21 Y/24 O	E stim; RIII Magnitude/ 5	R. Sural Nerve	0.33 Hz	0.14	0.58
Marouf, 2015	21 Y/24 O	E stim; RIII Magnitude/ 5	R. Sural Nerve	0.66 Hz	0.95	1.23
Marouf, 2015	21 Y/24 O	E stim; RIII Magnitude/ 5	R. Sural Nerve	1 Hz	1.64	1.57
Marouf, 2015	21 Y/24 O	E stim; RIII Magnitude/ 5	R. Sural Nerve	2 Hz	2.48	2.14

Note. A higher ES indicates a greater magnitude of TS. Y=younger; M=Middle-aged; O=older; ISI=Inter-stimulus interval; y=years; c=contact; ind.=individualized; L=Left; R=Right; Lat.=Lateral; Stim.=stimuli; E stim= electrical stimuli.

*Bulls, 2015 reported TS data for older and younger adults separately for non-Hispanic Whites (NHW) and African Americans (AA); thus effects sizes are presented for NHW's and AA's seperately.

Table 4. Summary of Results for studies examining age differences in TS: Within age group effects

TS: Within Group	# of Effects	Mean ES ± SD (95% CI's)	Unbiased ES	I^2
Younger vs. Older adults				
All				
Younger	40	0.55 ± 0.56 (0.38, 0.73)	0.51	69.1%
Older	40	0.72 ± 0.64 (0.52, 0.92)	0.66	78.0%
Heat TS				
Younger	14	0.24 ± 0.23 (0.12, 0.38)	0.25	5.1%
Older	14	0.31 ± 0.17 (0.21, 0.41)	0.31	0.0%
Electric TS				
Younger	20	0.68 ± 0.68 (0.36, 1.00)	0.64	70.4%
Older	20	0.85 ± 0.74 (0.51, 1.20)	0.81	74.3%
Punctate TS				
Younger	4	1.06 ± 0.05 (0.98, 1.13)	1.06	0.0%
Older	4	1.45 ± 0.31 (0.96, 1.94)	1.42	45.3%
Pressure TS				
Younger	2	0.42 ± 0.15 (-0.92, 1.75)	0.42	0.0%
Older	2	0.78 ± 0.06 (0.27, 1.29)	0.78	0.0%
Above 3-sec ISI				
Younger	12	0.19 ±0.25 (0.03, 0.35)	0.21	0.0%
Older	12	0.39 ±0.58 (0.02, 0.76)	0.40	0.0%
Below 3-sec ISI				
Younger	28	0.71 ± 0.51 (0.37, 1.01)	0.62	75.5%
Older	28	0.86 ± 0.62 (0.46, 1.24)	0.75	81.3%

Note. A higher ES indicates a greater magnitude of TS. SD=standard deviation;

CI=Confidence Interval; ISI=Inter-stimulus-interval. The unbiased ES are weighted by sample size.

Table 5. Studies examining age differences in CPM: Between group effects

Author, year	Sample Size (Younger/Older or Middle/Older)	Test Stimulus/ location	Conditioning Stimulus/loc	Concurrent Or not	Pooled ES
Edwards, 2003 [6]	37 Y (18-25 y)/ 40 O (55-67 y)	Heat TS / L. Hand	CWI- 5℃/ R. Hand	Concurrent	0.83
Lariviere, 2007 [17]	20 Y (20-35 y)/ 20 O (60-75 y)	HPT / Calf	CWI- 7℃/ R. Hand	Concurrent	0.60
Riley, 2010 [39]	27 Y (20-49 y)/ 22 O (56-77 y)	Pro. Heat / L. Palm	CWI ind.- 8-16℃/ R. Foot	Concurrent	0.81
Grashorn, 2013 [9]	22 Y (20-40 y)/ 25 O (61-80 y)	Mod. Heat / R. Forearm	CWI- 0℃/ L. Foot	Concurrent	0.93
Grashorn, 2013	22 Y/25 O	Mod. Heat / R. Forearm	CWI- 0℃/ L. Foot	Non-Concurrent	0.91
Lemley, 2015 [20]	20 Y (21.9±3.3 y)/ 19 O (72.0±4.5 y)	SPPT / Finger	CWI- 2℃/ Foot	Concurrent	1.22
Khan, 2018 [16]	106 Y (20-39 y)/ 20 O (60-80 y)	Mechanical TS/ Dominant Forearm	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.79
Khan, 2018	106 Y/ 20 O	Mechanical TS/ intraorrally	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.64
Khan, 2018	106 Y (20-39 y)/ 70 M (40-59 y)	Mechanical TS/ Dominant Forearm	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.28
Khan, 2018	106 Y/ 70 M	Mechanical TS/ intraorrally	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.20
Khan, 2018	70 M (40-59 y)/ 20 O (60-80 y)	Mechanical TS/ Dominant Forearm	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.50
Khan, 2018	70 M/ 20 O	Mechanical TS/ intraorrally	HWI- 46.5℃/ Non-dominant Hand	Concurrent	0.41
Lariviere, 2007 [17]	20 M (40-55 y)/ 20 O (60-75 y)	HPT / Calf	CWI- 7℃/ R. Hand	Concurrent	0.17
Grashorn, 2013 [9]	17 M (41-60 y)/ 25 O (61-80 y)	Mod. Heat/ R. Forearm	CWI- 0℃/ L. Foot	Concurrent	-0.23
Grashorn, 2013	17 M/25 O	Mod. Heat / R. Forearm	CWI- 0℃/ L. Foot	Non-Concurrent	0.01
Petersen, 2017 [33]	26 M (53-65 y)/ 24 O (66-79 y)	Pressure Cuff Tolerance/ Lower Leg	Pressure Cuff at 60 kPa/ Opposite Arm	Concurrent	-0.37

Note. A higher ES indicates greater CPM (Pain inhibition) for the younger group. Y=younger; M=Middle-aged; O=older; TS=temporal summation; y=years; L=left; CWI=cold water immersion; R-right; HPT=heat pain threshold; Pro.=prolonged; Mod.=moderate; SPPT= suprathreshold pressure pain test; s=seconds; loc=location; HWI=hot water immersion.

Table 6. Summary of Results for Age Differences in CPM between Younger Adults, Middle-aged, and Older adults

CPM: Between Group	# of Effects	Mean ES ± SD (95% CI's)	Unbiased ES	I^2
Younger vs. Middle-aged				
All	2	0.24 ±0.0.06 (-0.27, 0.75)	0.24	0%
Younger vs. Older adults				
All	8	0.84 ± 0.19 (0.68, 1.00)	0.80	0%
Concurrent or Non-concurrent Conditioning Stimulus				
Concurrent	7	0.83 ± 0.21 (0.64, 1.02)	0.79	0%
Non-Concurrent	1	0.91 ± 0.00 (NA)	NA	NA
Middle-aged vs. Older adults				
All	6	0.08 ± 0.35 (-0.28, 0.44)	0.17	30.9%
Concurrent or Non-concurrent Conditioning Stimulus				
Concurrent	5	0.10 ± 0.38 (-0.38, 0.57)	0.19	47.8%
Non-Concurrent	1	0.01 ± 0.00 (NA)	NA	NA

Note. A higher ES indicates younger/middle-aged adults had greater pain inhibition on the CPM test compared to older adults. The unbiased ES are weighted by sample size. NA=not applicable; SD=standard deviation; CI=Confidence Interval.

Table 7. Studies examining age differences in CPM: Within group effects

Author, year	Sample Size (Younger/Older or) Middle/Older)	Test Stimulus/ location	Conditioning Stimulus/location	Concurrent (C) Or not (NC)	Younger/ Middle ES	Older ES
Washington, 2000 [44]	15 Y (22-27 y)/ 15 O (67-87 y)	Electrical Threshold - 5Hz/ Dominant hand	CWI (2°C)/ Contra Hand	NC	1.26	0.45
Washington, 2000	15 Y/15 O	Electrical Threshold - 250Hz/ Dominant hand	CWI (2°C)/ Contra Hand	NC	1.95	0.52
Washington, 2000	15 Y/15 O	Electrical Threshold - 2000Hz/ Dominant hand	CWI (2°C)/ Contra Hand	NC	1.98	1.13
Washington, 2000	15 Y/15 O	Heat Threshold/ Dominant hand	CWI (2°C)/ Contra Hand	NC	1.45	0.37
Riley, 2010 [39]	27 Y (20-49 y)/ 22 O (56-77 y)	Prolonged heat / L. Palm	CWI (8-16°C) / R. Foot	C (Noxious v. neutral)	1.20	-0.16
Riley, 2010	27 Y/22 O	Prolonged heat / L. Palm	CWI (8-16°C) / R. Foot	C (Noxious v. no bath)	0.57	-0.42
Riley, 2010	27 Y/22 O	Prolonged heat / L. Palm	CWI (8-16°C) / R. Foot	NC	0.75	0.06
Naugle, 2015 [28]	24 Y (20-34 y)/ 19 O (55-77 y)	Heat REDSTIM / L. Palm	CWI (10°C M/12°C F) / R. Foot	NC	0.76	0.64
Lithfous, 2019 [22]	19 Y (22.4 y)/ 61 O (>60)	Heat Pain Threshold/ R. Hand	Cold Plate Contact (10°C)/ Palm of L. Hand	NC	0.72	-0.40
Graven-Nielsen, 2015 [10]	102 Y (18-44 y)/ 34 M (45-65 y)	Pressure cuff algo/ Non-dominant Leg	CWI (1-2°C)/ Dominant Hand	NC	0.10	0.75
Graven-Nielsen, 2015	102 Y (18-44 y)/ 34 M (45-65 y)	Pressure cuff algo/ Non-dominant Leg	CWI (1-2°C)/ Dominant Hand	NC	0.18	0.58

Note. A higher ES indicates greater CPM (Pain inhibition). L=left; y=years; CWI=cold water immersion;Contra=Contralateral; R-right; s=seconds; loc=location; L=left. REDSTIM=Response Dependent Stimulation; algo=algometry.

Table 8. Summary of Results for studies examining age differences in CPM: Within age group effects

CPM: Within Group	# of Effects	Mean ES ± SD (95% CI's)	Unbiased ES	I^2
Younger vs. Middle-aged				
Younger - All	2	0.14 ± 0.06 (-0.37, 0.65)	0.14	0.0%
Middle-aged – All	2	0.66 ± 0.12 (-0.41, 1.75)	0.66	0.0%
Younger vs. Older adults				
Younger - All	9	1.18 ± 0.53 (0.77, 1.60)	1.01	49.8%
Older – All	9	0.24 ± 0.52 (-0.15, 0.64)	0.10	60.1%
Non-Concurrent Conditioning Stimulus				
Younger - All	7	1.27 ± 0.55 (0.76, 1.78)	1.06	51.5%
Older – All	7	0.40 ± 0.48 (-0.05, 0.84)	0.38	13.8%
Concurrent Conditioning Stimulus				
Younger - All	2	0.88 ± 0.45 (-3.12, 4.89)	0.86	0.0%
Older – All	2	-0.29 ± 0.19 (-1.94, 1.36)	-0.29	0.0%

Note. A higher ES indicates greater CPM pain inhibition) for the younger group. The unbiased ES are weighted by sample size. SD=standard deviation; CI=Confidence Interval.

	Blind-ing	**Cases representative of population**			**Comparability of cases and controls**			**Known confounders**						**Total Score**
	Sub-score	Inclus. Criteria	Recruit-ment	***Sub-score***	Sex	Race	***Sub-score***	Menstr. cycle	Cognit. Impair.	Caff-eine	Meds	Pain Conds.	***Sub-score***	**0-8**
Graven-Nielsen, 2015 [10]	2	+	+	0	+	-	1	-	-	+	+	+	1	**4**
Edwards, 2003 [6]	2	+	+	0	-	+	1	-	-	-	+	+	2	**5**
Naugle, 2016a [26]	2	+	-	1	+	-	1	-	-	+	+	+	1	**5**
Naugle, 2016b [29]	2	+	+	0	+	-	1	-	-	+	+	+	1	**4**
Naugle, 2017 [27]	2	+	+	0	+	-	1	-	+	+	+	+	0	**3**
Lautenbacher, 2005 [19]	2	+	+	0	+	-	1	-	-	-	+	+	2	**5**
Farrell, 2007 [7]	2	+	+	0	+	+	0	-	+	-	+	+	1	**3**
Bulls, 2015 [1]	2	+	+	0	-	+	1	-	-	-	+	+	2	**5**
Marouf, 2015 [24]	2	+	+	0	-	-	2	-	+	+	+	+	0	**4**
Lariviere, 2007 [17]	2	+	+	0	+	-	1	-	+	+	+	+	0	**3**
Riley, 2010 [39]	2	+	+	0	+	-	1	-	+	+	+	+	0	**3**
Grashorn, 2013 [9]	2	+	+	0	+	-	1	-	-	-	+	+	2	**5**
Lemley, 2015 [20]	2	+	-	1	+	-	1	-	+	-	+	+	1	**5**
Washington, 2000 [44]	2	+	+	0	+	-	1	-	+	-	+	+	1	**4**
Naugle, 2015 [28]	2	+	+	0	-	-	2	-	-	+	+	+	1	**5**
Riley, 2019 [38]	2	+	+	0	+	-	1	-	+	+	+	+	0	**3**
Lithfous, 2019 [22]	2	+	+	0	+	-	1	-	+	-	+	+	1	**4**
Khan, 2018 [16]	2	+	-	1	-	-	2	-	-	-	+	+	2	**7**
Petersen, 2017 [33]	2	+	+	0	-	-	2	-	-	-	+	+	2	**6**

Table 9. Risk bias assessment of Studies

Note. Risk assessment is based on and adapted from the scale created by Lewis et al. (2012) in using meta-analysis to evaluate the efficacy of CPM in chronic pain conditions [21]. A higher score indicates higher risk of bias.