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Review article

Age changes in pain perception: A systematic-review and meta-analysis of age effects on pain and tolerance thresholds

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A B S T R A C T

Demographic changes, with substantial increase in life expectancy, ask for solid knowledge about how pain perception might be altered by aging. Although psychophysical studies on age-related changes in pain perception have been conducted over more than 70 years, meta-analyses are still missing. The present meta-analysis aimed to quantify evidence on age-related changes in pain perception, indexed by pain thresholds and pain tolerance thresholds in young and older healthy adults. After searching PubMed, Google Scholar and PsycINFO using state-of-art screening (PRISMA-criteria), 31 studies on pain threshold and 9 studies assessing pain tolerance threshold were identified. Pain threshold increases with age, which is indicated by a large effect size. This age-related change increases the wider the age-gap between groups; and is especially prominent when heat is used and when stimuli are applied to the head. In contrast, pain tolerance thresholds did not show substantial age-related changes. Thus, after many years of investigating age-related changes in pain perception, we only have firm evidence that aging reduces pain sensitivity for lower pain intensities.

Contents

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1. Introduction

Age changes in pain perception have been of growing interest for many years (Gagliese, 2009). Primary catalysts for this increasing interest have been the demographic changes in the developed countries, with substantial increases in life expectancy as well as high prevalence rates of clinical pain among older people (Gagliese, 2009). In parts due to these epidemiological phenomena, a number of experimental studies have accumulated over the years, in which age changes in pain perception – mainly in pain thresholds (PT) and pain tolerance thresholds (PTT) – have been studied in cross-sectional designs. These studies have repeatedly been reviewed (Edwards, 2005; Gibson and Farrell, 2004; Lautenbacher, 2012) and certain believes about the essential findings have been developed. For example, the pain threshold is supposed to increase with age whereas the tolerance threshold is assumed to decrease, which are two opposite changes that may, as a result, narrow the pain range in elderly individuals (Lautenbacher, 2012). Thus, on the one hand, age might dull the pain sense (at least for low pain intensities) as it dulls vision and audition; as a consequence, external threats may be detected later and older adults may run higher risks of injuries. On the other hand, older adults might tolerate strong pain intensities less well, possibly due to ineffective pain inhibitory processes. Consequently, pain complaints become more likely (Lautenbacher, 2012). Although the latter interpretation fits well with clinical findings of high pain prevalence rates in older adults (Gagliese, 2009), it is not undisputed because findings have repeatedly been contradictory (e.g. Cole et al., 2010; Edwards and Fillingim, 2001).

Given the great empirical interest in the topic, the sufficient number of relevant studies and the easy accessibility of the data, it is the rather surprising that meta-analytic attempts have been scarce and not published in peer-reviewed journals. Gibson (2003) previously published a meta-analysis in a book chapter. We presented in a review article (Lautenbacher, 2012) results from a meta-analysis being conducted as part of a Master Thesis. Although these meta-analytic results roughly corresponded with the narrative reviews, some ambiguities prevailed. These ambiguities mainly resulted from differences and inaccuracies as regards the weighting of studies according to the widely varying samples sizes, the statistical handling of strongly deviating results as well as inclusion criteria used for study selection. Therefore, the present meta-analysis aimed to quantify evidence on age-related changes in pain perception using a transparent and replicable operationalization. Furthermore, we tried to search for explanations for the differences between results of primary studies in a systematic fashion. To find possible moderators with explanatory value, we grouped the primary data into different categories that might be critical:

(i) The *mean age difference between the age groups* classified as young and old participants may matter. It is likely that the larger the age gap is, the more likely age effects on pain perception can be picked up even if linear relationships cannot be assumed. Thus, we categorized studies into those with small and those with large age gaps. (ii) The *type of physical stressor* (noxious stimulation based on temperature, pressure, electrical current, etc.) determines which nociceptive mechanisms are engaged, which time course and quality of pain sensations are associated and how physical threat is perceived by the individuals (Chapman et al., 1985; Gracely, 1999; Kumar Reddy et al., 2012). These factors may be differently affected by age, which makes the type of physical stressor chosen an important category to be considered. (iii) The *site of stimulation* determines which body tissue is stimulated. This in turn influences the nociceptor density in the stimulated area and the length of nociceptive fibers for impulse transmission from the periphery to the central nervous system. Even the psychological threat level can be affected by the site of stimulation because pain stimuli applied in the face are experienced as more threatening than at the lower limbs (Essick et al., 2004; Lautenbacher and Strian, 1991; Schmidt et al., 2016). These factors may undergo site-specific age changes, qualifying the site of stimulation as another relevant category for this meta-analysis.

In sum, the present meta-analysis aimed at determining age changes in pain perception indexed by changes in pain (PT) and tolerance thresholds (PTT). PT and PTT values were chosen as indicators of pain perception because they are psychophysical parameters – although not undisputed – of proven validity; furthermore, a sufficient number of primary studies are available investigating these variables in different age groups. Finally, it was examined whether the categorization of the primary studies according to (i) the mean age difference between groups (young and old participants), (ii) the type of physical stressor, and (iii) the site of stimulation, helps to explain differences between primary study outcomes.

2. Methods

The systematic review and meta-analysis were performed following the "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015" (Moher et al., 2015).

2.1. Search strategy and study selection

Literature search: An extensive search of literature published until January 2016 was conducted using the databases PubMed, Google Scholar and PsycINFO. We set no restrictions with regard to the earliest year of publication. In our search, we combined with a logical AND keywords for age (aging, aged, elderly, age difference, age related, geriatric, gerontolo*, senior, older; connected with a logical OR) with keywords for experimental pain sensitivity (pain threshold, pain tolerance; connected with a logical OR).[1] Given that we were interested in age-related changes in pain sensitivity, which occur in older age and are not confounded by age-related diseases, we excluded the following keywords by setting a NOT qualification: child, adolescen*, pediatric, neonat*, fetal, disease, intervention. Additionally, reference lists from identified articles and reviews on pain and aging (Gibson and Farrell, 2004; Lautenbacher, 2012) were screened for missing articles. The systematic search was limited to human subjects and articles published in English.

Eligibility criteria: We selected only those studies (i) that assessed pain and/or tolerance thresholds, (ii) that reported the chronological age of the participants, (iii) that included at least two age groups, (iv) with one of the age groups having a mean age >60 years and (v) an age difference of at least 10 years between age groups (mean difference), (vi) with a minimum sample size of $N = 20$, (vii) and that provided a clear description of statistics. Furthermore, we only included studies focussing on healthy participants and, thus, we excluded studies of populations restricted to specific diseases, pathological conditions, or metabolic disorders as well as studies where participants took medications that could alter the processing of pain (analgesics, psychotropic drugs). Thus, the selected data should be representative for true non-pathological aging effects on pain sensitivity. We excluded non-original research, conference proceedings, and doctoral theses. Two independent reviewers (MH, JS) screened the titles and abstracts for the eligibility criteria. We retrieved full texts of all studies that were potentially relevant or where exclusion could not be determined based on the study title or abstract. In case of discrepancies/disagreement between the 2 reviewers, a third

[1] Precise search terms and combinations are available from the authors upon request.

reviewer (SL) was consulted and discrepancies/disagreement were resolved.

2.2. Data extraction

Data were extracted by one reviewer (JS) and documented in a data extraction form; the extracted data were independently counter-checked by a second reviewer (SL). Study characteristics (e.g. sample size, historical age, age difference between groups, gender distribution), pain induction methods (physical type of pain, scale unit of threshold, site of stimulation) and outcome measures (pain threshold and/or pain tolerance threshold data) were recorded. All ambiguities in data extraction were double-checked and resolved. In case of repeated measurements, we tried to assess data averaged over time; if this was not possible, we used the data from the first time point. If the required information could not be retrieved from the published article, up to 3 e-mails were sent out to the corresponding author or the co-authors to request the information. In case of no response after 3 e-mails, we ceased attempting to receive the data. Altogether, we attempted to contact the authors in 8 cases and were able to receive data in 5 cases.

2.3. Assessing the quality of studies

There are no standardized criteria to assess the quality of psychophysical studies on experimental pain. Thus, we reviewed recent meta-analyses with psychophysical outcome parameters and adopted a suitable system of quality assessment based on earlier publications, e.g. Tesarz et al. (2012) and on the Newcastle Ottowa criteria (Wells et al., 2000). We assessed the quality by use of six criteria, which were (i) reported gender distribution in each age-group, (ii) similar gender distribution for all age-groups, (iii) specification of stimulus location, (iv) specification of physical type of stimulus, (v) report on psychophysical method of threshold determination and (vi) the extent to which the study population represents the true population (in our case: healthy elderly individuals). Each criterion was judged as either "successfully fulfilled" (1), "partially fulfilled (0.5) or "not fulfilled" (0). A study had to reach at least a quality score of 4.0.

Furthermore, we assessed risk of publication bias by visually inspecting funnel plots and calculating Begg–Mazumdar Kendall's τ (Begg and Mazumdar, 1994) (based on continuity-corrected normal approximation) and Egger's bias test (Egger et al., 1997).

2.4. Statistical analyses

As effect size measure, we applied Hedges' g, because the more common Cohen's d has a bias to overestimate the effect sizes in small samples. This bias is corrected for in Hedges' g. All analyses used the random-effects model, because from a theoretical point of view, one cannot expect (as is done in the fixed-effect model) that all effect differences between studies are due to sampling errors and not, at least partly, due to differences in the true effect sizes (Borenstein et al., 2010; Hedges and Vevea, 1998). Moreover, as a consequence of using the random-effects model, the relative weight that is assigned to any study is more balanced over studies with varying sample sizes, preventing studies with relatively large samples from gaining unjustified influence on the summary effect.

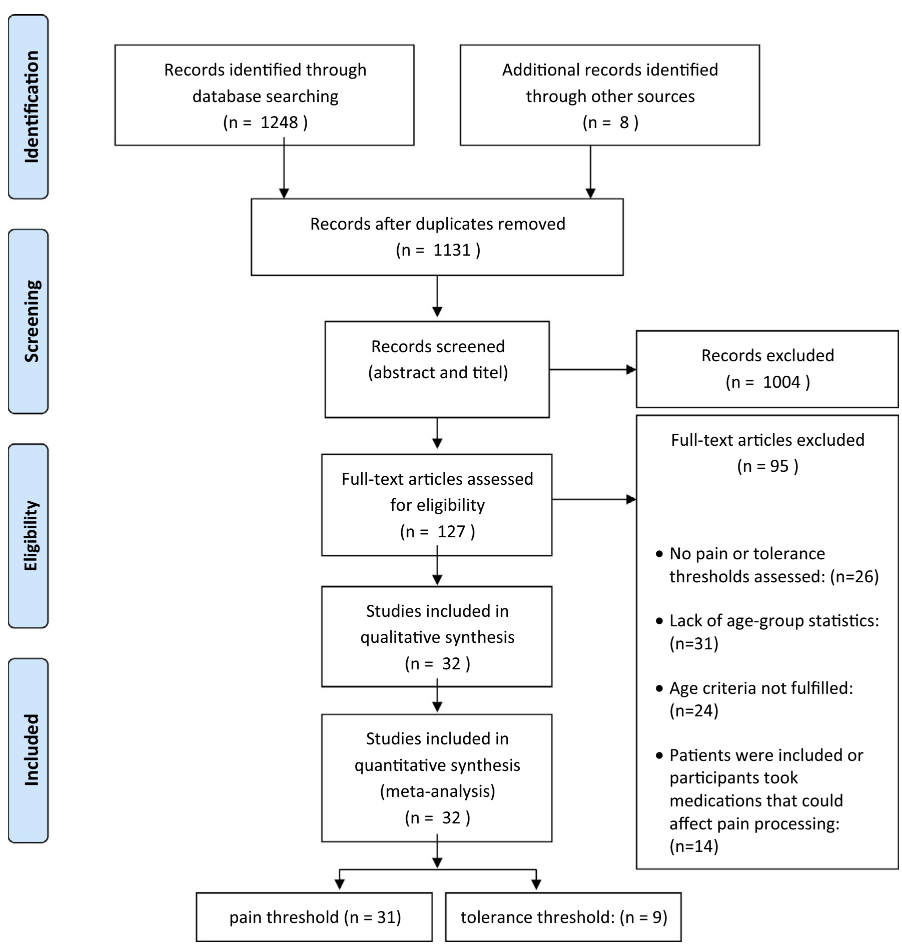

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram. Study selection process.

In case, studies included multiple groups of older individuals (e.g. age-groups 60–69, 70–79 years), which were always compared with the same group of young participants, we selected the largest group of older participants and discarded the other groups of older individuals. This was the case in nine studies assessing pain threshold (Da Silva et al., 2014; Heft et al., 1996; Jensen et al., 1992; Lariviere et al., 2007; Magerl et al., 2010; Neziri et al., 2010; Procacci et al., 1970; Sherman and Robillard, 1964; Yarnitsky et al., 1995) and in one study assessing pain tolerance (Woodrow et al., 1972). Reducing the number of groups with older individuals to one was necessary in order to avoid statistical dependencies that would give an unjustified high weight to studies with multiple comparison groups.

In order to assess whether variability in effect sizes might be due to (i) the "*mean age difference between age groups*", we run a Knapp–Hartung random-effects meta-analysis, estimating τ^2 with the method of moments approach (Knapp and Hartung, 2003). Moreover, given that we expected that the "*type of physical stressor*" (e.g. heat, pressure) as well as the "*site of stimulation*" (e.g. head, arm) might also explain variability in effect sizes, we conducted subgroup analyses for (ii) the different types of physical stressor applied as well as for (iii) the different sites of stimulation.

All analyses were conducted with the program Comprehensive Meta-Analysis Version 3.3 (Borenstein et al., 2014).

3. Results

3.1. Characteristics of included studies

The initial literature search identified 1284 studies with 8 additional studies found through manual searching of reference lists. The study selection process is displayed in Fig. 1. After excluding duplicates and screening the remaining abstracts and titles, 127 studies remained. After reviewing the full texts of these remaining articles, 95 articles were excluded. The reasons for exclusion are listed in Fig. 1. Altogether 32 articles were retained for analyses, with 31 studies assessing pain thresholds (see Table 1) and 9 studies assessing pain tolerance thresholds (see Table 3) in young and older healthy individuals. All of these studies also met our quality criteria (as defined in the method section) and reached quality scores ≥4.0 (see Table 1). Altogether, pain threshold data allocated 1558 young (771 females, 787 males) and 1354 older individuals (724 females, 630 males). Pain tolerance data (despite fewer studies) included even larger sample sizes, namely 5694 young (3623 females, 2071 males) and 5601 older individuals (3290 females, 2311 males). This was due to the very large sample size included in Woodrow et al. (1972).

3.2. Publication bias

There was no evidence of substantial publication bias, neither for the pain threshold studies (Begg $\tau = 0.15$, $p = .12$ [one-tailed]; Egger test intercept = 1.73, $p = .18$ [one-tailed]) nor for the tolerance threshold studies (Begg $\tau = -0.08$, $p = .38$ [one-tailed]; Egger test intercept = 0.84, $p = .19$ [one-tailed]).

3.3. Age differences in pain threshold (PT)

3.3.1. Overall effect

Thirty-one studies reported differences in pain thresholds for a younger compared to an older participant group (see Table 1 and Fig. 2). The average PT was significantly increased in older individuals (>60 years) compared to younger individuals ($g = 0.818$ (95% CI: 0.450–1.187), $Z = 4.350$, $p < .001$). Thus, the overall analysis of age effects on PT estimates suggests a reduced sensitivity to pain in older individuals with a strong effect size.

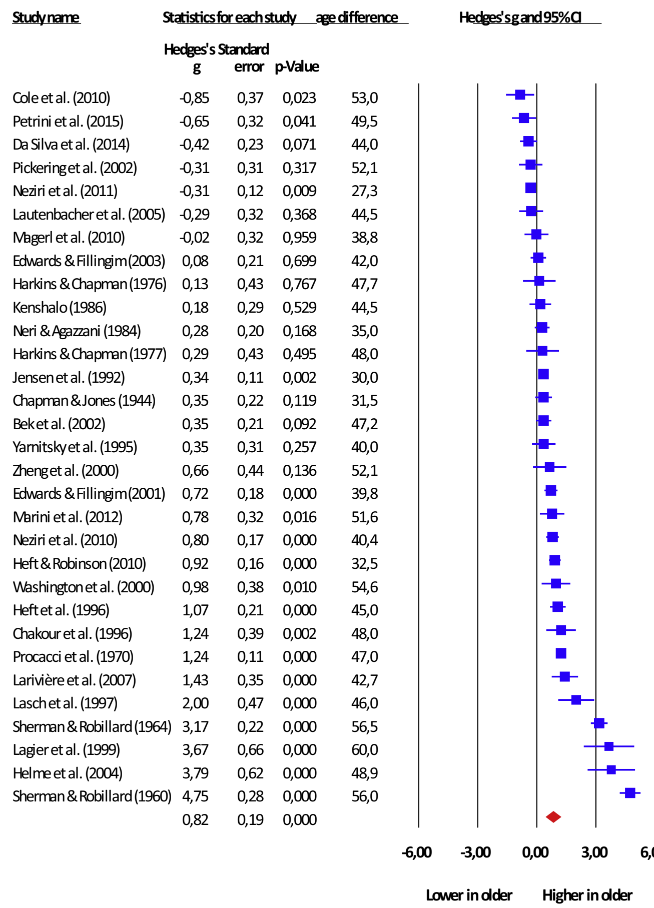

Fig. 2. Forest plot of age effects on pain thresholds (PT). The size of the squares reflects the relative weight of this study within its subgroup.

(i) Mean age difference between the age group: To further investigate this age-effect on PT, we tested whether this age-effect varies depending on the age gap between age groups. Or in other words, did we find larger age differences in pain thresholds, the further apart in years the two age groups were? To answer this question, a Knapp–Hartung random-effects meta-regression was run, estimating τ^2 with the method of moments approach. As shown in Fig. 3, age-differences in PT did indeed increase the greater the age difference between age groups was. The slope of 0.0691 (95% CI: 0.0267–0.1237) is significant, $t(29) = 2.59$, $p = .015$, R^2 analog = .235 (Goodness of fit: $T^2 = .762$, $I^2 = 93.45\%$, $Q(29) = 442.90$, $p < .001$).

3.3.2. Analyses considering subcategories

(ii) Type of physical stressor: In the analysis of the type of physical stressor, we included 31 studies with 39 effects (eight studies used different sites of stimulation). For this exploratory subgroup meta-analysis, we again applied a random-effects model; the meta-effects are shown in Table 2. This exploratory analysis revealed that age-effects on PT differed significantly depending on the type of physical stressor applied, with a heterogeneity of $Q(6) = 32.937$, $p < .001$. Older individuals showed increased pain thresholds when thermal (heat) stimuli were used (especially thermode and radiation) (see Table 2), whereas electrical and pressure stimulation did not yield this clear age-dependent increase in pain thresholds. We also found significant effects for rectal and esophageal distensions; however these findings were only based on a single study. When computing single comparisons to directly compare effect sizes between single type of stressors, effect sizes for thermal (heat)

Table 1
Primary studies included in the meta-analysis of pain threshold (PT).

Study	Young (*N*)	Old (*N*)	Mean age difference between age groups (years)	Type of physical stressor	Site of stimulation	Quality score of the study (range 0–6)
Bek et al. (2002)	40	60	47.2	Pressure	Arm, leg	4.5
Chakour et al. (1996)	15	15	48.0	Thermal(l)	Arm	5.5
Chapman and Jones (1944)	20	20	31.5	Thermal(r)	Head	4.5
Cole et al. (2010)	15	15	53.0	Pressure	Arm	5.5
Da Silva et al. (2014)	41	28	44.0	Pressure Electrical	n.s. Head	5.0
Edwards and Fillingim (2001)	34	34	39.8	Thermal(t) Pressure	Arm Head, trunk	5.5
Edwards et al. (2003)	45	48	42.0	Thermal(t)	Arm	5.5
Harkins and Chapman (1976)	10	10	47.7	Electrical	Head	4.5
Harkins and Chapman (1977)	10	10	48.0	Electrical	Head	4.5
Heft et al. (1996)	49	54	45.0	Thermal(t)	Head	5.0
Heft and Robinson (2010)	92	86	32.5	Thermal(t)	Head	5.0
Helme et al. (2004)	15	15	48.9	Thermal(t), electrical	Arm	5.5
Jensen et al. (1992)	178	144	30.0	Pressure	Head	6.0
Kenshalo (1986)	27	21	44.5	Thermal(t)	Arm, leg	5.0
Lagier et al. (1999)	12	12	60.0	Rectal distension	Visceral	4.5
Lasch et al. (1997)	10	17	46.0	Esophageal distension	Visceral	4.5
Lariviere et al. (2007)	20	20	42.7	Thermal(t)	Leg	6.0
Lautenbacher et al. (2005)	20	20	44.5	Thermal(t), pressure	Arm	5.5
Magerl et al. (2010)	60	12	38.8	Thermal(t), pressure	Leg, arm, head	5.5
Marini et al. (2012)	20	20	51.6	Pressure	Head, arm	5.5
Neri and Agazzani (1984)	50	50	35.0	Electrical	Arm	5.0
Neziri et al. (2010)	75	75	40.4	Electrical	Leg	5.5
Neziri et al. (2011)	150	150	27.3	Thermal(t), pressure	Leg, trunk, arm	6.0
Petrini et al. (2015)	20	20	49.5	Pressure	Arm, trunk	5.5
Pickering et al. (2002)	21	21	52.1	Thermal(t), pressure	Arm	5.5
Procacci et al. (1970)	258	139	47.0	Thermal(r)	Arm	4.5
Sherman and Robillard (1960)	90	110	56.0	Thermal(r)	Head	4.0
Sherman and Robillard (1964)	90	90	56.5	Thermal(r)	Head	4.0
Washington et al. (2000)	15	15	54.6	Electrical, thermal(l)	Arm	5.5
Yarnitsky et al. (1995)	46	13	40.0	Thermal(t)	Leg, arm	5.0
Zheng et al. (2000)	10	10	52.1	Pressure	Arm	5.0
Sum of participants	**1.558**	**1.354**				

Type of physical stressor: thermal(t) = thermode; thermal(l) = laser; thermal(r) = radiation.
Site of stimulation: head: including teeth and neck; arm: including hand; leg: including foot; visceral: rectum, esophagus; n.s. = not specified.

stimulation differed significantly from effect sizes for pressure stimulation (pressure vs. "thermal: laser": $Q(1) = 10.516$, $p = .001$; pressure vs. "thermal: radiation": $Q(1) = 19.021$, $p < .001$; pressure vs. "thermal: thermode": $Q(1) = 3.441$, $p = .064$ (marginally significant)). Most other comparisons between stimulation types were not significant. In sum, the type of physical stressor does have a substantial effect on age-differences in PT, with older individuals showing reduced sensitivity mostly to thermal (heat) pain stimulation.

(iii) Site of stimulation: In the analysis of the site of stimulation, we included 31 studies with 43 effects (nine studies used different sites of stimulation). For this exploratory subgroup meta-analysis,

Table 2
Exploratory subgroup analyses for age-effects on pain thresholds (PT).

Type of subcategories	No of studies	No of subjects (young/old)	Effect size (Hedges' *g*) 95% CI	Test for the subgroup effect (*p* value)
Type of physical stressor				
Electrical	7	216/263	0.66 (SE 0.34)	.053
Pressure/Mechanical	12	609/534	0.003 (SE 0.25)	0.990
Thermal: laser	2	30/30	1.27 (SE 0.65)	0.051
Thermal: radiation	4	458/359	2.34 (SE 0.43)	**<0.001**
Thermal: thermode	12	587/486	0.53 (SE 0.26)	**0.037**
Rectal distension	1	12/12	3.67 (SE 1.06)	**0.001**
Esophageal distension	1	10/17	2.00 (SE 0.96)	**0.037**
Site of stimulation				
Arm/hand	18	861/678	0.41 (SE 0.23)	.082
Head	12	702/610	0.89 (SE 0.28)	**.002**
Leg/foot	7	418/351	0.28 (SE 0.37)	.446
Trunk	3	204/204	−0.28 (SE 0.56)	.621
Visceral	2	22/29	2.76 (SE 0.78)	**<.001**
Various areas	1	41/28	0.46 (SE 0.97)	.635

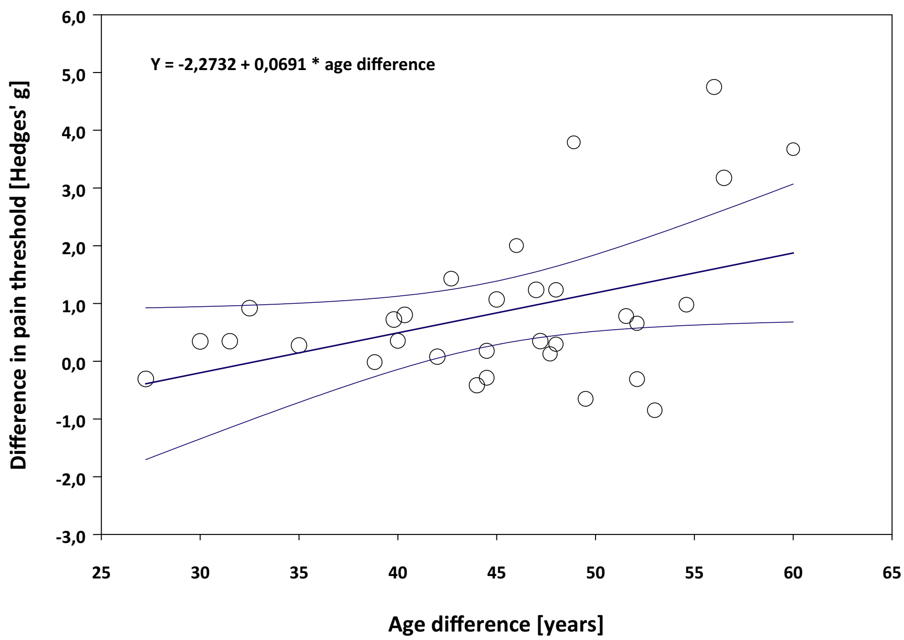

Fig. 3. Method of moments meta-regression to assess whether the difference between age groups affects age-effects on PT. The difference in pain thresholds is calculated as the pain threshold of the older minus the pain threshold of the younger age group (i.e., positive values indicate that older people have higher pain thresholds). In addition to the regression line, confidence intervals are shown. The circle size reflects the weight obtained by a study in this meta-regression.

we applied a random-effects model. The meta-effects for the different sites of stimulation are shown in Table 2. This exploratory analysis revealed, that age-effects on PT differed significantly depending on the site of stimulation, with a heterogeneity of $Q(5) = 12.721$, $p = 0.026$. Older individuals showed increased pain thresholds when stimuli were applied to visceral sites or in the head area (see Table 2); whereas other sites of stimulation did not yield this clear age-dependent increase in pain thresholds.

However, when computing single comparisons to directly compare effect sizes between single stimulation sites, the difference was only marginal. Indeed, the effect sizes for "head area" did not differ from effect sizes of other stimulation sites. Only effect sizes for "visceral sites" differed from other stimulation sites (arm/hand, leg/foot, trunk; all $p < .001$), however, it has to be mentioned that only 2 studies applied visceral pain. In sum, the site of stimulation only marginally affects age-differences in PT.

3.3.3. *Summary of age-effects on pain thresholds*

Pain thresholds are affected by age, with older individuals (>60 years) showing increased PT compared to younger individuals. Since Hedges' *g* is 0.82, the effect can be considered large. This difference increases the greater the age difference between age groups is. Moreover, this age-dependent increase in PT mainly manifests itself when using heat pain stimulation and – to a smaller degree – when considering stimulation at the head.

3.4. *Age differences in pain tolerance threshold (PTT)*

3.4.1. *Overall effect*

Nine studies reported differences in tolerance thresholds for a younger compared to an older participant group (see Table 3 and Fig. 4). The average PTT did not differ significantly between age groups, however, the difference was close to significance ($g = -0.237$ (95% CI: -0.479 to 0.005), $Z = 1.921$, $p = .055$).

(i) Mean age difference between the age group: As we did for PT effects, we tested whether age-effects on PTT might vary depending on the age gap between age groups. Again, a Knapp–Hartung random-effects meta-regression was run, estimating τ^2 with the method of moments approach. As shown in Fig. 5, the magnitude of the mean age difference between groups did not substantially affect

Table 3
Primary studies included in the meta-analysis of pain tolerance threshold (PTT).

Study name	Young (*N*)	Old (*N*)	Mean age difference between age groups (years)	Type of physical stressor	Site of stimulation	Quality score of the study (range 0–5)
Bek et al. (2002)	40	60	47.2	Pressure	n.s.	4.5
Edwards and Fillingim (2001)	34	34	39.8	Thermal(t), pressure	Arm	4.5
Edwards et al. (2003)	45	48	42.0	Thermal(t)	Arm	4.5
Neri and Agazzani (1984)	50	50	35.0	Electrical	Arm	4.5
Neziri et al. (2011)	150	150	27.3	Thermal(t), pressure	Leg, trunk, arm	5.0
Petrini et al. (2015)	20	20	49.5	Pressure	Arm, trunk	5.0
Pickering et al. (2002)	21	21	52.1	Thermal(t), pressure	Arm	5.0
Washington et al. (2000)	15	15	54.6	Thermal(t)	Arm	4.5
Woodrow et al. (1972)	5319	5203	40.0	Pressure	Leg	4.5
Sum of participants	**5694**	**5601**				

Type of physical stressor: thermal (t) = thermode.
Site of stimulation: arm: incl. hand; leg: incl. foot; n.s. = not specified.

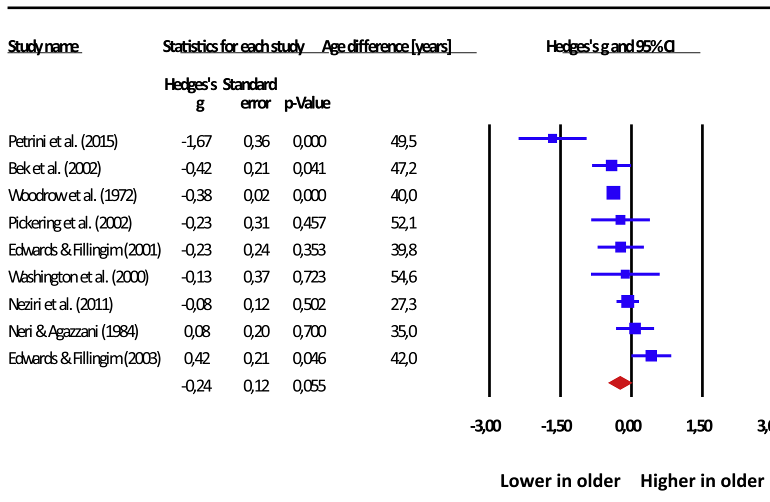

Fig. 4. Forest plot of age effects on pain tolerance thresholds (PTT). The size of the squares reflects the relative weight of this study within its subgroup.

the pain tolerance outcomes. The slope of −0.020 was not significant (95% CI: −0.068 to 0.028), $t(7) = 0.998$, $p = .352$, R^2 analog = .001 (Goodness of fit: $T^2 = .087$, $I^2 = 78.40\%$, $Q(7) = 32.41$, $p < .001$).

3.4.2. Subcategory analyses

Despite the non-significant main effect of age on PTT, we wanted to investigate whether the age-effects might vary dependent on the site of stimulation and type of physical stressor used.

(ii) Type of physical stressor: In this analysis, we included nine studies with 12 effects (three studies used two sites of stimulation). For this exploratory subcategory meta-analysis, we again applied a random-effects model. The meta-effects for the different types of physical stressors are shown in Table 4. There was no significant amount of heterogeneity between meta-effects for the different types of physical stressor ($Q(2) = 4.465$, $p = .107$). Despite this lack of significant heterogeneity, this exploratory analysis revealed that using pressure stimuli is accompanied by a significant age-related reduction in tolerance threshold (see Table 4), whereas other types of physical stressors did not show any age-related effects. Nevertheless, given the non-significant amount of heterogeneity between types of physical stressors used, one must conclude that overall the type of physical stressor does not have a substantial effect on age-differences in PTT.

(iii) Site of stimulation: In this analysis, we included 9 studies with 12 effects (two studies used different areas of stimulation). For this exploratory subgroup meta-analysis, we applied a random-effects model. The meta-effects for the different sites of stimulation are shown in Table 4. There was no significant amount of heterogeneity between meta-effects for the four sites of stimulation, $Q(3) = 1.685$, $p = .640$. Accordingly, sites of stimulation do not have an effect on age-differences in PTT.

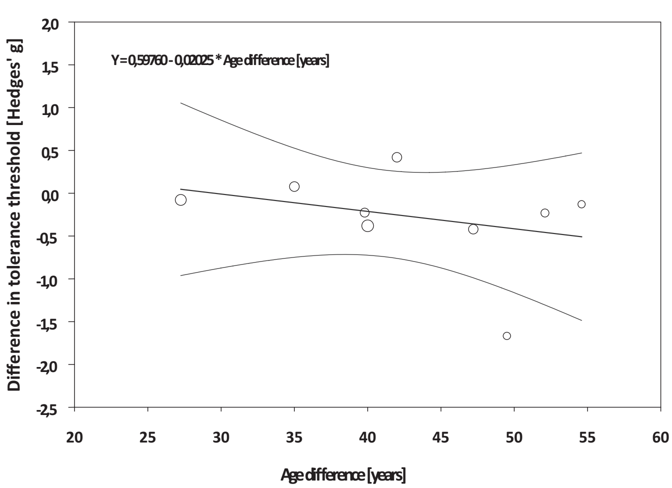

Fig. 5. Method of moments meta-regression to assess whether the difference between age groups affects age-effects on PTT. The difference in pain tolerance thresholds is calculated as the tolerance threshold of the older minus the tolerance threshold of the younger age group (i.e., positive values indicate that older people have a higher tolerance threshold). In addition to the regression line, confidence intervals are shown. The circle size reflects the weight obtained by a study in this meta-regression.

3.4.3. Summary of age-effects on tolerance thresholds

Pain tolerance thresholds are almost unaffected by age. Although there is a tendency for older individuals (>60 years) to show slightly reduced tolerance thresholds compared to younger individuals, this age-effect only becomes significant when using pressure pain stimulation to assess PTT. The study of Petrini et al. (2015) clearly deviates from the rest of the studies (see Fig. 4). However, even the removal of this study does not change the results with the only exception that effect of the physical stressor for pressure/mechanical changed from significant ($g = -0.420$, $p = 0.009$) to not significant ($g = -0.263$, $p = .073$).

4. Discussion

The main result of the present meta-analysis is that pain thresholds (PT) increase with age. The number of studies was sufficient for meta-analysis and the mean effect size revealed a large age effect on PT. Therefore, the conclusion of dulled sensitivity for low pain intensities in elderly adults stands on solid ground. Finding that this age effect increased the larger the mean age difference between age groups was, corroborates the assumption that advanced age is associated with reduced pain sensitivity in the lower pain range.

This age-related change appeared to gain physiological substance when heat stimulation was used as physical stressor whereas the changes for pressure and electrical current as pain stimuli were negligible. The heat-related nociceptors are mainly situated in the superficial tissue and the pain response is mediated by C-fibers when radiation and contact heat is used for stimulation (Fowler et al., 1988; Yarnitsky and Ochoa, 1991), as was frequently the case in the included studies. This component of nociception has mainly exteroceptive function and warns the individual about

Table 4
Exploratory subgroup analyses for age-effects on pain tolerance thresholds (PTT).

Type of subgroups	No of studies	No of subjects (young/old)	Effect size (Hedges' *g*) 95% CI	Test for the overall effect (*p* value)
Type of physical stressor				
Electrical	1	50/50	0.08 (SE 0.38)	.841
Pressure/Mechanical	6	5584/5488	−0.42 (SE 0.16)	**.009**
Thermal: thermode	5	265/268	0.06 (SE 0.18)	.732
Site of stimulation				
Arm/hand	7	335/338	−0.18 (SE 0.17)	.296
Leg/foot	2	5469/5353	−0.28 (SE 0.27)	.296
Trunk	2	170/170	−0.63 (SE 0.31)	**.044**
Various areas	1	40/60	−0.42 (SE 0.43)	.327

imminent physical threat from the outer world (Price et al., 2003). Age seems to dull this exteroceptive function and leaves the individual at a higher risk of experiencing bruises, injuries and burns (Lautenbacher, 2012). In this sense, "presbyalgos" may develop as other reductions of sensory functions with increasing age, comparable to age-dependent loss in vision ("presbyopia") and hearing ("presbyacusis"). There also are a lot of examples in the literature showing a decline of somatosensory functions (warmth, cold, touch, vibration) with age (Deshpande et al., 2008; Guergova and Dufour, 2011; Lin et al., 2005; Yarnitsky and Sprecher, 1994). The application of heat stimuli has emerged to be especially appropriate to demonstrate an age-related decline in pain sensitivity. In accord, nociceptive laser- and contact-heat evoked brain potentials have also appeared to decrease with age (Chao et al., 2007; Gibson et al., 1991; Truini et al., 2005). Moreover, the heat pain specific activation in the insula and the somatosensory cortex is reduced in elderly individuals as functional imaging (fMRI) studies could show (Quiton et al., 2007; Tseng et al., 2013).

Finding no age-effects on PT when pressure or electrical current were applied, might be due to different mechanisms of peripheral sensory encoding because deep tissue nociceptors are also involved in case of pressure pain and receptor-mechanisms are largely bypassed in case of painful stimulation with electrical current while Aδ-fibers are directly activated (Chapman et al., 1985; Kumar Reddy et al., 2012). The lack of age changes in electrical PT is in line with two studies in which the Nociceptive Flexion Reflex (NFR) was assessed. In both studies the NFR was elicited using electrical current. Neither the NFR threshold nor the NFR amplitude were different between young and aged participants (Farrell and Gibson, 2009; Mylius et al., 2008). Pressure as well as electrical current were both applied as stimuli in an investigation on age changes in facial responses to pain, again with negative results (Kunz et al., 2008). Thus, objective pain measures corroborate the negative findings as regards age changes in pain thresholds assessed by use of pressure and electrical current as stimuli.

The substantial difference between age changes in pressure and heat pain sensitivity was also found in study on neural responses to pain using fMRI (Cole et al., 2010). Whereas pressure pain revealed age-related changes in the striatal region; heat pain stimulation was differently processed by young and older participants in the insula and somatosensory cortex.

Visceral stimulation also produced large effect sizes, with an increase in pain threshold with advanced age in two studies (stimulation in the esophagus and rectum). However, the number of studies is too little for firm conclusions. A much more relevant finding is the accumulation of positive findings when the stimulation was applied to areas of the head, including soft tissue and teeth. As it stands, the finding suggests a stronger affection by age of the trigeminal than the spinal nociceptive system (Dubner and Bennett, 1983). The limited number of studies did unfortunately not allow for a systematic comparison of soft tissue and tooth stimulation for different age-related changes. It is tempting to see a relationship between this decline in pain sensitivity and the decrease in prevalence of soft tissue-related cranial pain conditions like tension-type headache (Kaniecki, 2006; Reinisch et al., 2008) and temporomandibular pain disorder (LeResche, 1997), which is unparalleled by similar age changes of tooth pain (Riley and Gilbert, 2001). This potential relationship should be followed up in future studies. Interestingly, the present meta-analysis does not corroborate the distal-proximal development of age-related changes, as found in other somatosensory modalities (with early affection of the lower limbs and later affection of the upper limbs and trunk; Lin et al., 2005), for the pain system. It is assumed that age-related dying-back axonopathies affect sensory nerve fibers supplying the lower extremities earlier than shorter sensory nerve fibers supplying other parts of the body (Shaffer and Harrison, 2007). According to our data, this kind of aging mechanism does very likely not become active in the nociceptive system. To the best of our knowledge, there is no hypothesis put forward so far to explain a higher vulnerability for age changes in the trigeminal compared to the spinal nociceptive system.

In earlier reviews about age changes, the assertion was made that in parallel to the increase in pain threshold there is also a decrease in pain tolerance threshold (Lautenbacher, 2012). These two opposing age-related trends were supposed to narrow the whole pain range. Furthermore, there were speculations about an age-related loss of sensory pain processing (pain threshold related) and an enhancement of affective pain processing (pain tolerance threshold related) (Lautenbacher, 2012). Given our meta-analysis results, the effect of aging on PT could be based on a sufficient number of studies with large enough effect sizes to be called significant whereas the evidence for age changes in PTT was weak to non-existent. The previous notion that pain tolerance thresholds decrease with aging was mainly based on the decline of PTT when pressure was used in one study with a huge sample of over 40,000 participants (Woodrow et al., 1972), which gained enormous weight in former secondarily published meta-analyses (Gibson, 2003; Lautenbacher, 2012) and in the opinion of former reviewers. We did not analyze all age groups (groups between 30 and 59 years of age were not analyzed) but only two age groups from the study by Woodrow et al., namely a group of young participants (20–29 years, $n = 5319$) and a group of older participants (60–69 years, $n = 5203$), to limit an unduly influence of this study. The resulting 10,522 participants from the Woodrow study still represent more than 90% of all subjects studied for age changes in pain tolerance. The effect of Hedges' $g = -0.38$ from this study was not sufficient to lead to an overall significant age effect on PTT across studies (Hedges' $g = -0.24$).

Furthermore, although pain threshold and pain tolerance threshold are correlated by definition (pain tolerance threshold = pain threshold + pain range), the shared age-related covariance was too little (close to zero) in the present study to produce in parallel positive findings for age changes in both thresholds; in other words, the positive age finding for the pain threshold could not entail a similar finding for the pain tolerance threshold. In addition, autonomic reactions to pain like heart rate (HR) and sympathetic skin responses (SSR), which are sometimes thought to be physiological correlates of the affective responses to pain, rather decline than increase in aged individuals (Mylius et al., 2008; Kunz et al., 2009a). Such results do not indicate stronger affective responding in old age as a decreased pain tolerance threshold may suggest.

Thus, the belief of age-related changes in pain tolerance thresholds cannot be based on solid ground. In order to come to a firm conclusion, more than the nine available studies on age-related changes of pain tolerance thresholds are urgently needed.

There are two limitations as regards the findings of age-related increase in pain thresholds, which ought to be mentioned. (i) The collection of data spans now across a period of more than 70 years (Chapman and Jones, 1944). The experimental methods for pain assessment and the techniques of pain induction have considerably improved during this time. Furthermore, the health status of similar age cohorts has also dramatically changed to the better (Fogel, 2003). Therefore, the data basis may have undergone hidden historical changes, which may invalidate our "unhistorical" conclusions. To secure our conclusions of age effects on PT against this bias, we run a regression analysis with the historical age of the study as predictor and the effect size as criterion (presented in the supplementary material to this article). The result was a significant effect with a tendency towards lower effect sizes over the years. However, this effect was small enough to keep the conclusion of an increase of pain threshold with aging valid. The second limitation refers to the age of the older participants. Although the age gap between young and older adults in the studies included was mostly more than 4 decades, the older adults were rarely above 80 and the average age of this age group was often well below 70 years. Thus, "old olds" were seldom and "oldest olds" were almost never under study. However, especially these individuals belong to the fastest growing age segments of the populations in developed countries (Ortman et al., 2014). Furthermore, they substantially constitute those persons at risk for developing dementia, which is a pathological condition with a well-known impact on the pain system (Achterberg et al., 2013; Kunz et al., 2009b). Thus, future studies should attempt to include these very aged individuals without age-related pathologies.

In conclusion, after many decades of psychophysical research on age changes in pain perception, we know for certain that there is a loss of pain sensitivity in the lower pain range, which is indicated by an increase of pain thresholds in older adults. This reduced pain sensitivity mainly becomes manifest when heat is used for the induction of pain. Age effects on pain tolerance could not be substantiated in the present meta-analysis. Although these changes have often both been claimed in the past, the evidence for an age-related decrease in pain tolerance threshold is much weaker than that for an increase in pain threshold. Approaches with supra-threshold pain ratings, pain-evoked brain potentials, brain imaging and other objective pain measures have been too scarce to be subjected to meta-analysis. Since it is widely agreed that knowledge about age changes in the pain system is mandatory because of the demographic changes taking place, the relatively small number of studies in this field is surprising and calls for further action. Future studies should ideally investigate age changes in pain perception by testing different sites and using different methods of pain assessment (types of physical stressor, threshold and supra-threshold parameters) in young, old and oldest old individuals.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.01.039.

References

Achterberg, W.P., Pieper, M.J., van Dalen-Kok, A.H., de Waal, M.W., Husebo, B.S., Lautenbacher, S., Kunz, M., Scherder, E.J.A., Corbett, A., 2013. Pain management in patients with dementia. Clin. Interv. Aging 8, 1471–1482.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Bek, N., Uygur, F., Bayar, B., Armutlu, K., 2002. Analysis of age and gender related differences in pressure pain threshold and pressure pain tolerance levels. Pain Clin. 14 (4), 309–314.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Meth. 1, 97–111.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2014. Comprehensive Meta-Analysis (Version 3.3.070) [Computer Software]. Biostat., Englewood, NJ, Available from: http://www.meta-analysis.com.

Chakour, M.C., Gibson, S.J., Bradbeer, M., Helme, R.D., 1996. The effect of age on Aδ and C-fibre thermal pain perception. Pain 64 (1), 143–152.

Chao, C.C., Hsieh, S.T., Chiu, M.J., Tseng, M.T., Chang, Y.C., 2007. Effects of aging on contact heat-evoked potentials: the physiological assessment of thermal perception. Muscle Nerve 36 (1), 30–38.

Chapman, C.R., Casey, K.L., Dubner, R., Foley, K.M., Gracely, R.H., Reading, A.E., 1985. Pain measurement: an overview. Pain 22 (1), 1–31.

Chapman, W.P., Jones, C.M., 1944. Variations in cutaneous and visceral pain sensitivity in normal subjects. J. Clin. Investig. 23 (1), 81.

Cole, L.J., Farrell, M.J., Gibson, S.J., Egan, G.F., 2010. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. Neurob. Aging 31 (3), 494–503.

Da Silva, L.A., Lin, S.M., Teixeira, M.J., Siqueira, J.T.T., Jacob Filho, W., Siqueira, S.R.D.T., 2014. Sensorial differences according to sex and ages. Oral Dis. 20 (3), e103–e110.

Deshpande, N., Metter, E.J., Ling, S., Conwit, R., Ferrucci, L., 2008. Physiological correlates of age-related decline in vibrotactile sensitivity. Neurob. Aging 29 (5), 765–773.

Dubner, R., Bennett, G.J., 1983. Spinal and trigeminal mechanisms of nociception. Ann. Rev. Neurosci. 6 (1), 381–418.

Edwards, R., 2005. Age-associated differences in pain perception and pain processing. In: Gibson, S., Weiner, D. (Eds.), Pain in Older Persons: Progress in Pain Research and Management. IASP Press, Seattle, pp. 45–66.

Edwards, R.R., Fillingim, R.B., 2001. Age-associated differences in responses to noxious stimuli. J. Gerontol. A: Biol. Sci. Med. Sci. 56 (3), M180–M185.

Edwards, R.R., Fillingim, R.B., Ness, T.J., 2003. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 101 (1), 155–165.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Essick, G., Guest, S., Martinez, E., Chen, C., Mcglone, F., 2004. Site-dependent and subject-related variations in perioral thermal sensitivity. Somatosens. Mot. Res. 21 (3–4), 159–175.

Farrell, M., Gibson, S., 2009. Age interacts with stimulus frequency in the temporal summation of pain. Pain Med. 8 (6), 514–520.

Fogel, R.W., 2003. Changes in the process of aging during the twentieth century: findings and procedures of the early indicators project (No. w9941). In: National Bureau of Economic Research.

Fowler, C.J., Sitzoglou, K., Ali, Z., Halonen, P., 1988. The conduction velocities of peripheral nerve fibres conveying sensations of warming and cooling. J. Neurol. Psychiatry 51, 1164–1170.

Gagliese, L., 2009. Pain and aging: the emergence of a new subfield of pain research. J. Pain 10 (4), 343–353.

Gibson, S.J., 2003. Pain and aging: the pain experience over the adult life span. In: Dostrovsky, J.O., Carr, D.B., Koltzenburg, M. (Eds.), Proceedings of the 10th World Congress on Pain. IASP Press, Seattle, pp. 767–790.

Gibson, S.J., Farrell, M., 2004. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin. J. Pain 20 (4), 227–239.

Gibson, S.J., Gorman, M.M., Helme, R.D., 1991. Assessment of pain in the elderly using event-related cerebral potentials. In: Bond, M.R., Charlton, J.E., Woolf, C.J. (Eds.), Proceedings of the VIth World Congress on Pain. Elsevier, Amsterdam, pp. 523–529.

Gracely, R.H., 1999. Studies of pain in human subjects. In: Wall, P.D., Melzack, R. (Eds.), Textbook of Pain. , 4th ed. Churchill Livingstone, Edinburgh, pp. 385–408.

Guergova, S., Dufour, A., 2011. Thermal sensitivity in the elderly: a review. Ageing Res. Rev. 10 (1), 80–92.

Harkins, S.W., Chapman, C.R., 1976. Detection and decision factors in pain perception in young and elderly men. Pain 2 (3), 253–264.

Harkins, S.W., Chapman, C.R., 1977. The perception of induced dental pain in young and elderly women. J. Geront. 32 (4), 428–435.

Hedges, L.V., Vevea, J.L., 1998. Fixed- and random-effects models in meta-analysis. Psychol. Methods 3, 486–504.
Heft, M.W., Robinson, M.E., 2010. Age differences in orofacial sensory thresholds. J. Dental Res. 89 (10), 1102–1105.
Heft, M.W., Cooper, B.Y., O'Brien, K.K., Hemp, E., O'Brien, R., 1996. Aging effects on the perception of noxious and non-noxious thermal stimuli applied to the face. Aging Clin. Exp. Res. 8 (1), 35–41.
Helme, R.D., Meliala, A., Gibson, S.J., 2004. Methodologic factors which contribute to variations in experimental pain threshold reported for older people. Neurosci. Lett. 361 (1), 144–146.
Jensen, R., Rasmussen, B.K., Pedersen, B., Lous, I., Olesen, J., 1992. Cephalic muscle tenderness and pressure pain threshold in a general population. Pain 48 (2), 197–203.
Kaniecki, R.G., 2006. Tension-type headache in the elderly. Curr. Pain Headache Rep. 10 (6), 448–453.
Kenshalo, D.R., 1986. Somesthetic sensitivity in young and elderly humans. J. Gerontol. 41 (6), 732–742.
Knapp, G., Hartung, J., 2003. Improved tests for a random effects meta-regression with a single covariate. Stat. Med. 22, 2693–2710.
Kumar Reddy, K.S., Naidu, M.U.R., Rani, P.U., Rao, T.R.K., 2012. Human experimental pain models: a review of standardized methods in drug development. J. Res. Med. Sci. 17 (6), 587.
Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., 2008. Impact of age on the facial expression of pain. J. Psychosom. Res. 64 (3), 311–318.
Kunz, M., Mylius, V., Scharmann, S., Schepelman, K., Lautenbacher, S., 2009a. Influence of dementia on multiple components of pain. Eur. J. Pain 13 (3), 317–325.
Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., 2009b. Effects of age and mild cognitive impairment on the pain response system. Gerontology 55 (6), 674–682.
Lagier, E., Delvaux, M., Vellas, B., Fioramonti, J., Bueno, L., Albarede, J.L., Frexinos, J., 1999. Influence of age on rectal tone and sensitivity to distension in healthy subjects. Neurogastroenterol. Motil. 11 (2), 101–108.
Lariviere, M., Goffaux, P., Marchand, S., Julien, N., 2007. Changes in pain perception and descending inhibitory controls start at middle age in healthy adults. Clin. J. Pain 23 (6), 506–510.
Lasch, H., Castell, D.O., Castell, J.A., 1997. Evidence for diminished visceral pain with aging: studies using graded intraesophageal balloon distension. Am. J. Physiol. Gastrointest. Liver Physiol. 272 (1), G1–G3.
Lautenbacher, S., 2012. Experimental approaches in the study of pain in the elderly. Pain Med. 13 (s2), S44–S50.
Lautenbacher, S., Strian, F., 1991. Sex differences in pain and thermal sensitivity: the role of body size. Percept. Psychophys. 50 (2), 179–183.
Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., Arendt-Nielsen, L., 2005. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 115 (3), 410–418.
LeResche, L., 1997. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit. Rev. Oral Biol. Med. 8 (3), 291–305.
Lin, Y.H., Hsieh, S.C., Chao, C.C., Chang, Y.C., Hsieh, S.T., 2005. Influence of aging on thermal and vibratory thresholds of quantitative sensory testing. J. Peripher. Nerv. Syst. 10 (3), 269–281.
Magerl, W., Krumova, E.K., Baron, R., Tölle, T., Treede, R.D., Maier, C., 2010. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. Pain 151 (3), 598–605.
Marini, I., Bortolotti, F., Bartolucci, M.L., Inelmen, E.M., Gatto, M.R., Bonetti, G.A., 2012. Aging effect on pressure pain thresholds of head and neck muscles. Aging Clin. Exp. Res. 24 (3), 239–244.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4 (1), 1.
Mylius, V., Kunz, M., Hennighausen, E., Lautenbacher, S., Schepelmann, K., 2008. Effects of ageing on spinal motor and autonomic pain responses. Neurosci. Lett. 446 (2–3), 129–132.
Neri, M., Agazzani, E., 1984. Aging and right–left asymmetry in experimental pain measurement. Pain 19 (1), 43–48.
Neziri, A.Y., Andersen, O.K., Petersen-Felix, S., Radanov, B., Dickenson, A.H., Scaramozzino, P., Arendt-Nielsen, L., Curatolo, M., 2010. The nociceptive withdrawal reflex: normative values of thresholds and reflex receptive fields. Eur. J. Pain 14 (2), 134–141.
Neziri, A.Y., Curatolo, M., Nüesch, E., Scaramozzino, P., Andersen, O.K., Arendt-Nielsen, L., Jüni, P., 2011. Factor analysis of responses to thermal, electrical, and mechanical painful stimuli supports the importance of multi-modal pain assessment. Pain 152 (5), 1146–1155.
Ortman, J.M., Velkoff, V.A., Hogan, H., 2014. An Aging Nation: The Older Population in the United States. US Census Bureau, Washington, DC, pp. 25–1140.
Petrini, L., Matthiesen, S.T., Arendt-Nielsen, L., 2015. The effect of age and gender on pressure pain thresholds and suprathreshold stimuli. Perception 44 (5), 587–596.
Pickering, G.E.L., Jourdan, D., Eschalier, A., Dubray, C., 2002. Impact of age, gender and cognitive functioning on pain perception. Gerontology 48 (2), 112–118.
Price, D.D., Greenspan, J.D., Dubner, R., 2003. Neurons involved in the exteroceptive function of pain. Pain 106 (3), 215–219.
Procacci, P., Bozza, G., Buzzelli, G., Corte, M.D., 1970. The cutaneous pricking pain threshold in old age. Gerontol. Clin. 12 (4), 213–218.
Quiton, R.L., Roys, S.R., Zhuo, J., Keaser, M.L., Gullapalli, R.P., Greenspan, J.D., 2007. Age-related changes in nociceptive processing in the human brain. Ann. N. Y. Acad. Sci. 1097, 175–178.
Reinisch, V.M., Schankin, C.J., Felbinger, J., Sostak, P., Straube, A., 2008. Headache in the elderly. Der. Schmerz. 22 (1), 22–30.
Riley, J.L., Gilbert, G.H., 2001. Orofacial pain symptoms: an interaction between age and sex. Pain 90 (3), 245–256.
Schmidt, K., Forkmann, K., Sinke, C., Gratz, M., Bitz, A., Bingel, U., 2016. The differential effect of trigeminal vs. peripheral pain stimulation on visual processing and memory encoding is influenced by pain-related fear. NeuroImage 134, 386–395.
Shaffer, S.W., Harrison, A.L., 2007. Aging of the somatosensory system: a translational perspective. Phys. Therap. 87 (2), 193–207.
Sherman, E.D., Robillard, E., 1960. Sensitivity to pain in the aged. CMAJ 83 (18), 944–947.
Sherman, E.D., Robillard, E., 1964. Sensitivity to pain in relationship to age. J. Am. Geriatr. Soc. 12 (11), 1037–1044.
Tesarz, J., Schuster, A.K., Hartmann, M., Gerhardt, A., Eich, W., 2012. Pain perception in athletes compared to normally active controls: a systematic review with meta-analysis. Pain 153 (6), 1253–1262.
Truini, A., Galeotti, F., Romaniello, A., Virtuoso, M., Iannetti, G.D., Cruccu, G., 2005. Laser-evoked potentials: normative values. Clin. Neurophysiol. 116 (4), 821–826.
Tseng, M.T., Chiang, M.C., Yazhuo, K., Chao, C.C., Tseng, W.Y., Hsieh, S.T., 2013. Effect of aging on the cerebral processing of thermal pain in the human brain. Pain 154 (10), 2120–2129.
Washington, L.L., Gibson, S.J., Helme, R.D., 2000. Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain 89 (1), 89–96.
Wells, G.A., Shea, B., O'connell, D., Peterson, J.E.A., Welch, V., Losos, M., Tugwell, P., 2000. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (November 2016).
Woodrow, K.M., Friedman, G.D., Siegelaub, A.B., Collen, M.F., 1972. Pain tolerance: differences according to age, sex and race. Psychosom. Med. 34 (6), 548–556.
Yarnitsky, D., Ochoa, J.L., 1991. Warm and cold specific somatosensory systems. Psychophysical thresholds, reaction times and peripheral conduction velocities. Brain 114, 1819–1826.
Yarnitsky, D., Sprecher, E., 1994. Thermal testing: normative data and repeatability for various test algorithms. J. Neurol. Sci. 125, 39–45.
Yarnitsky, D., Sprecher, E., Zaslansky, R., Hemli, J.A., 1995. Heat pain thresholds: normative data and repeatability. Pain 60 (3), 329–332.
Zheng, Z., Gibson, S.J., Khalil, Z., Helme, R.D., McMeeken, J.M., 2000. Age-related differences in the time course of capsaicin-induced hyperalgesia. Pain 85 (1), 51–58.