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Running title: pain and aging

The effect of age and gender on pressure pain thresholds and suprathreshold stimuli

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Abstract

Objectives: The study investigates the impact of age and gender on (1) experimental pressure pain detection (PPDT) and tolerance (PPTolT) thresholds (2) participants' self-reports of pain intensity and unpleasantness at supra- and sub-threshold level.

Methods: 20 young: 20-34 (24.6 ± 3.5 years, 10 F) and 20 elderly: 65-88 (73.7 ± 6.6 years, 10 F) healthy volunteers were compared. Mini-Mental State Examination (MMSE 28-30) assessed intact cognitive functioning. Pain thresholds were assessed together with the sensory intensity ratings to 1.3 x PPDT (pain) and 0.2 x PPDT (no-pain).

Results: PPDT and PPTolT were significantly decreased with age and were lower in young females as compared with young males. No gender differences were observed in the elderly group. PPDT decreased significantly with age in males but not in females. Conversely, the intensity and unpleasantness of the pain stimulus were significantly rated lower in the elderly as compared with the young. No gender differences were observed in the report of intensity and unpleasantness of the stimulations.

Discussion: A mismatch in pain sensitivity, tolerance and pain self' reports was observed. Findings suggest that pain experience in the elderly differ from the experience in the younger on multiple dimensions: sensory, affective and cognitive. Findings may also indicate that elderly appraise pain experience using different psychological strategies.

Key words: Experimental pain, elderly, gender, pain perception, cognitive functioning

Running title: pain and aging

1. Introduction

Pain is a very common problem for elderly people. Epidemiological studies have indicated that the experience of persistent and chronic pain becomes more prevalent and disabling in elderly people (Helme and Gibson, 2001). In addition, aging is generally associated with greater expectations of pain, more pain sites, and the development of other chronic disorders associated with pain (Gibson et al., 1994). However, other evidences have also suggested that there is a reduction in the frequency of pain complaints in elderly (Parmelee et al, 1993; Gagliese et al., 1999; Galiese and Melzack, 1997) as a result pain often goes under-recognized and under-treated in the elderly (Herr and Garand, 2001). In addition, the tools available for assessing pain in the elderly are insufficiently developed. Self-report is the gold standard for assessing pain. However, in many clinical circumstances with elderly, such as with those who have cognitive impairment, the patient's self-report is unobtainable due to verbal communications problems or fear of the consequence of acknowledging pain (Herr and Garand, 2001). This of course has negative impacts on their health and quality of life, unnecessary suffering, and physical and psychological disabilities.

Experimental pain studies have shown variability in pain sensitivity in elderly individuals when these are compared with young individuals, and the findings of these studies are contradictory with each other. Studies using heat stimuli have shown increased pain thresholds (Gibson et al., 1991; Lautenbacher and Strian, 1991) whereas studies using mechanical pressure and ischemic pain stimuli have reported decreased pain thresholds (Gibson and Farrell, 2004; Pickering et al., 2002; Lautenbacher et al., 2005; Edwards and Fillingim, 2001). Studies using noxious electrical stimulations have reported no age-related differences in pain sensitivity

(Gibson and Farell, 2004). Furthermore, experiments examining age differences in pain tolerance thresholds have shown that elderly withdraw from noxious stimuli at lower intensities as compared with their younger counterparts (Gibson and Farrell, 2004). Thus, variability on pain sensitivity could be due to the fact that different pain stimulations trigger different neural processes that do not age uniformly (Farrell, 2012; Chakour et al., 1996; Gagliese et al., 2006). To date, experimental research has focused mostly at the level of pain threshold and very limited knowledge is available on age-related changes in pain sensitivity at suprathreshold level (Gibson and Farrell, 2004). Investigating suprathreshold responses is also important because it elucidates pain sensitivity along the stimulus-response function. If advancing age is associated with decreases in the acuity at suprathreshold level then older people could be more at risk of injury (Gibson and Farrell, 2004). Earlier studies using a controversial signal detection theory (SDT) approach (Rollman, 1977) showed age-related differences in reporting the intensity of suprathreshold noxious stimuli. The results showed that elderly subjects were less willing to rate low-intensity stimuli as painful, whereas they were more willing to rate high intensity stimuli as painful (Harkins and Chapman, 1976; 1977; Harkins et al., 1986). More recent studies also showed that older individuals rated suprathreshold CO2-laser stimulations as less painful and less unpleasant than young individuals (Chakour et al., 1996; Gibson et al., 1991). However, opposite findings were observed in other studies where thermal stimuli were utilized (Heft et al., 1996; Edwards and Fillingim, 2001). Whereas no age differences on pain ratings for heat and pressure stimuli were observed with regard to suprathreshold spatial summation (Lautenbacher et al., 2005). Few experimental studies (Lautenbacher et al., 2005; Pickering et al., 2002) have investigated the direct influence of gender on age related changes in pain perception. Since gender difference

play an important role in pain perception in young and middle age the present investigation wants to contribute to the understanding of gender difference in older age.

The aim of the present study was to investigate the effects of aging on 1) pressure pain sensitivity at threshold (detection and tolerance), 2) supra-threshold (self-report intensity/unpleasantness) level in a group of healthy young (aged 20-34) and elderly (aged 65-88) individuals, and 3) the interaction between age and gender on pain sensitivity at threshold and suprathreshold level. Sub-threshold sensitivity was also included to compare perception response in the non-pain domain.

2. Methods

2.1 Subjects

Twenty young healthy volunteers between the ages of 20 and 34 years (mean age 24.6 ± 3.6 years) and 20 healthy elderly volunteers between the ages of 65 and 88 years (mean age 73.6 ± 6.6 years) participated in the study. Each age group consisted of 10 male and 10 female subjects. Participants were recruited via posted advertisements and their participation was volunteered. Young subjects were mainly recruited amongst University students whereas elderly subjects were recruited from recreational centers. Participants were screened with an interview prior participation to exclude conditions that could affect pain perception and pain report. Exclusion criteria were: if the participant reported the presence of severe ongoing pain, neuropsychological and psychiatric disorders, diabetes, signs of rheumatic or arthritic disease especially on hand/fingers and neck/shoulders. During the interview, subjects were also tested with the Mini Mental State Examination (MMSE) in order to ensure cognitive intact capabilities; consequently only subjects that scored in the range of (28-30) were

included in the study. Furthermore, all subjects were pain-free and none of them had taken any analgesic or sedative for at least 48h prior to the experiment. The study protocol was approved by the regional ethics committee (ID-201310613).

2.2 Apparatus

2.2.1 Pressure stimuli

An electronic hand-held pressure algometer (Somedic AB, Stockholm, Sweden) was used to produce noxious mechanical pressure. A force gauge fitted with a rubber disk with a surface of 1 cm^2 was used in this study.

2.3 Procedure

The experiment took place in a quiet and climate-controlled room, where the subjects were seated in a comfortable chair. All subjects were familiarized with the test procedure and were trained until they understood the procedure and were able to follow the instructions before testing started.

2.3.1 Pressure Pain Detection Threshold (PPDT)

PPDT was defined as the minimal pressure (kPa), which the subjects first perceived as painful. The subject pushed a button to stop the pressure stimulation when the threshold was reached. The probe (1 cm^2) was placed perpendicular to the skin and pressure was applied (30 kPa/s) until the participant pressed a button when the pertinent threshold was reached. PPDT was measured four times and the mean of these four measurements was used.

PPDT was determined on four body sites: index fingers left and right; trapezius muscle left and right.

The individual pain detection threshold (PPDT) was then used to calculate supra-threshold pain and sub-threshold no-pain stimulations for each subject.

2.3.2 Pressure Pain Tolerance Threshold (PPTolT)

PPTolT tolerance was defined as the point at which the pressure became unbearable painful to be felt. Participants were instructed to *"try to take as much pain as you possibly can"*. The subject pushed a button to stop the pressure stimulation when the tolerance threshold was reached. The cut-off limit was set as 1960 kPa.

PPTolT was determined on two sites: left index finger and left trapezius muscle.

2.3.3. Supra-threshold Pain and Sub-threshold No-Pain stimulations

Supra-threshold pain and sub-threshold no-pain stimulations were determined for each subject on the base of the individual pain detection threshold (PPDT). Pain stimuli were calculated as 1.3 X PPDT and no-pain stimuli as 0.2 x PPDT.

Each pain and no-pain stimulus was applied twice on four body sites: index fingers left and right; and trapezius muscle left and right. A total of sixteen stimulations were randomly applied on the fingers (both sides) and trapezius (both sides). To avoid possibility of tissue damage each stimulus was applied for 5sec.

2.3.4. Numerical Rating Scale (NRS)

Supra- and sub-threshold sensitivity was measured using a numerical rating scale (NRS). Participants' ratings of pain intensity and pain unpleasantness to supra-threshold and sub-threshold pressure were recorded after each stimulus.

The intensity and unpleasantness of the stimulus were respectively rated using two 0-10 numerical rating scales (NRS), which were posted in front of the participants.

The intensity ratings were measured using a modified numerical rating scale (NRS) that combined both innocuous sensory range and noxious sensory range. The intensity rating scale was ranging from 0 (no sensation) to 10 (the worst pain you can imagine), where level 4 was set as pain detection threshold. A similar scale was used in the

authors' previous work (Petrini et al., 2014). The unpleasantness rating scale was ranging from 0 (no unpleasant) to 10 (unbearable unpleasant). Before the experiment started, the experimenter introduced the two rating scales to the subject and explained the conceptual distinction between intensity and unpleasantness dimensions of pain. Instructions were similar to the ones used by previous authors (Price et al., 1983; Reinville et al., 1992).

2.3.5 Data analyses

Data were statistically analyzed using SPSS version 22.0. All data are given as means ±SEM.

The effects of age, gender, and body site on pain detection and tolerance thresholds were evaluated using mixed-design ANOVAs with two between-subjects factors (age and gender) and one within-subject factor (body site).

To evaluate the effect of age, gender and body site on supra-threshold pain and sub-threshold no-pain intensity and unpleasantness ratings, mixed-design ANOVAs with two between-subjects factors (age and gender) and one within-subject factor (body site) was also conducted.

In all ANOVA analyses, a Bonferroni's correction when testing for multiple comparison and a Greenhouse-Geisser correction to adjust the degrees of freedom when the sphericity level was < 0.05 were used.

In case of significant results, pairwise comparisons were conducted using post-hoc Bonferroni tests. The level of significance was set to $P \leq 0.05$.

3. Results

3.1 Pain Detection Thresholds

There were significant main effects for the factors: *age* [$F(1,36)=10.45$, P=0.003; partial $\eta^2= 0.23$], *gender* [$F(1,36)=14.48$, P=0.001, partial $\eta^2= 0.29$], and *body site* [$F(2.104,108)=10.97$, P<0.001, partial $\eta^2=0.23$]. A two-way interaction involving: *age x body site* [$F(2.104, 108)= 0.45$, P=0.648, partial $\eta^2=0.01$] and gender x body site [$F(2.104, 108)= 2.53$, P=0.084, partial $\eta^2=0.06$] were not significant. A three way-interaction *age x gender x body site* [$F(2.104, 108)= 0.35$, P=0.713, partial $\eta^2=0.01$] was also not significant. Data showed a significant two way interaction in: *age x gender* [$F(1,36)=5.26$, P=0.02, partial $\eta^2=0.12$].

Post-hoc analyses revealed also that within the male group age had an effect since PDT resulted significantly lower in the male elderly subjects as compared with the male young subjects (P<0.001). This effect was not significant in the female group (P=0.25). A significant effect was also observed within the young subjects since PDT was lower in female as compared with male (P<0.001), this effect was not significant in the elderly group (P=0.06).

Furthermore, a significantly higher PDT was observed on the left finger (P<0.001). Data are shown in figure 1.

Insert figure 1 near here

3.2 Pain Tolerance Thresholds

There were significant main effects for the factors: *age* [$F(1,36)=48.27$, P<0.001, partial $\eta^2=0.57$] and *gender* [$F(1,36)=16.37$, P<0.001, partial $\eta^2=0.31$]; whereas the main effect *body site* [$F(1,36)=2.185$, P=0.148, partial $\eta^2=0.05$] was not significant.

A two-way interaction involving: *age x body site* [$F(1,36)= 0.12$, P=0.914, partial $\eta^2=0.00$] and gender x body site [$F(1,36)= 0.195$, P=0.662, partial $\eta^2=0.00$] were not significant.

A three way-interaction *age x gender x body site* [$F(1,36)= 0.004$, P=0.949, partial $\eta^2=0.00$] was also not significant.

Data showed a significant two way interaction in: *age x gender* [$F(1,36)=9.83$, P=0.003, partial $\eta^2=0.21$].

Post-hoc analyses revealed also that within the male and female groups age had an effect since PTT resulted significantly lower in the male elderly subjects (P<0.001) and in female subjects (P<0.05) as compared with the male and female young subjects.

A significant difference was also observed within the young subjects. PTT was lower in female as compared with male (P<0.001). This effect was not significant in the elderly subjects (P=0.39).

Data are shown in figure 2.

Insert figure 2 near here

3.3 Supra/sub-threshold ratings: Pain and No-Pain Intensities (NRS)

In regards with pain intensity ratings, there was only a significant main effect for the factor *age* [$F(1,36)=16.58$, P<0.001, partial $\eta^2=0.31$]. The other main effects *gende*r [$F(1,36)=0.003$ P=0.96, partial $\eta^2=0.00$] and *body site* [$F(1,108)=1.550$, P=0.21, partial $\eta^2=0.14$] were not significant. The interactions were also not significant: *body site* x *age* [$F(3, 108)= 1.701$, P=0.17, partial $\eta^2=0.04$], *body site* x *gender* [$F(3, 108)=$

2.061, P=0.11, partial η^2=0.05], *age x gender* [*F*(1,36)=0.061, P=0.81, partial η^2=0.05], and *body site* x *age* x *gender* [*F*(3, 108)= 0.281, P=0.83, partial η^2=0.00]. In regards with no-pain intensity ratings, no significant effects were observed. Data are shown in Figure 3a.

Insert figure 3 near here

3.4 Supra/sub-threshold ratings: Pain and No-Pain Unpleasantness (NRS)

In regards with pain unpleasantness ratings, there were significant main effects for the factor *age* [*F*(1, 36)= 15.658, P<0.001, partial η^2=0.30] and *body site* [*F*(3, 108)= 2.6, P<0.05, partial η^2=0.20]. The main factor *gender* [*F*(3, 108)= 1.579, P=0.19, partial η^2=0.20] and the interactions *body site* x *age* [*F*(3, 108)= 0.409, P=0.75, partial η^2=0.01], *body site* x *gender* [*F*(3, 108)= 1.579, P=0.19, partial η^2=0.04], *age x gender* [*F*(1,36)= 0.013, P=0.91, partial η^2=0.00], and *body site* x *age* x *gender F*(3, 108)= 0.598, P=0.61, partial η^2=0.01] were not significant.

Post-hoc analyses showed that finger left had higher unpleasantness ratings as compared with finger right (P<0.05).

In regards with no-pain unpleasantness ratings, no significant effects were observed. Data are shown in Figure 4.

Insert figure 4 near here

4. Discussions

The present study showed a mismatch in pain sensitivity depending on the outcome measure utilized. Elderly participants showed higher pain sensitivity when testing for

both pain detection and tolerance thresholds whereas they reported lower subjective pain ratings (NRS) when tested with supra-threshold pain stimuli. Gender difference was visible in thresholds sensitivity and it was prevalent in the young subjects while it disappeared in the elderly.

4.1 Pain Thresholds

The present study showed reduced pressure pain thresholds in the elderly as compared with younger individuals.

So far, experimental results on pain threshold in elderly have shown inconsistent results with reports that pain threshold increases, decreases, or does not change with aging (Gagliese and Melzack, 1997). The diversity of results can be attributed to the use of different methodological approaches. In fact, differential aging effect has been demonstrated using different stimulus modality, different stimulus duration, and different body sites of application (Gibson and Farrell, 2004; Lautenbacher, 2012). Despite these differences, the majority of the studies applying pressure pain stimulations have found reduced pressure pain thresholds in elderly as compared with younger individuals (Pickering et al., 2002; Lautenbacher et al., 2005; Edwards and Fillingim, 2001; Cole et al., 2010). However, a single study found an increase in pressure pain thresholds (Jensen et al., 1992). Researchers have pointed out to a possibility of reduction in endogenous pain inhibition in elderly individuals (Edwards et al., 2003; Washington et al., 2000; Larivière et al., 2007; Cole et al., 2010), hypothesizing that an age-related decrease in threshold would constitute a maladaptive warning capacity of the pain system (Gibson and Farrell, 2004). A change in pressure sensitivity could also be attributed to progressive degenerative changes in skin and muscle that accompanies aging.

Age-related enhancement in pressure pain sensitivity is quite relevant since it is more likely for elderly to develop musculoskeletal pain (Helme and Gibson, 2001). Although, musculoskeletal pain is a common symptom it is often under-reported and inadequately treated in older adults (Lillie et al., 2013). This is an important clinical problem to be addressed in the future and more research is needed to support this aspect.

Differential thresholds effects have also been attributed to different body sites (Gibson and Farrell, 2004); however, the present study did not observe differences in pressure sensitivity between the different body sites examined (finger and trapezius both left and right sides). However, differential effects of age as function of body sites have been reported when comparing for example foot with hand (Lautenbacher and Strian, 1991; Meliala et al., 1991).

4.2 Pain Supra-thresholds

The present study showed that elderly participants rated the intensity and the unpleasantness of suprathreshold stimuli significantly lower than younger participants. However, these results seem inconsistent with the decreased detection and tolerance thresholds observed in the elderly group as compared with the younger group and hence other factors may be involved. However, the pattern of results is consistent with the data from previous studies where elderly individuals have the tendency to rate suprathreshold stimuli as less intense (Harkins and Chapman, 1976; 1977; Harkins et al., 1986). It has been suggested that elderly may be more reluctant than younger individuals to report painful stimuli. Studies using the signal detection theory (SDT) methodology found that elderly adopted a more conservative response

bias than younger individual when labeling noxious stimuli (Harkins and Chapman; 1976) claiming that an age-related change in the willingness to report pain might exist. Although the SDT methodology has been criticized the results might point to possible mechanisms. In fact, psychological factors such as attitudes and beliefs about pain play a very important role in influencing the patients' report and experience of pain. Few studies have pointed out to the importance of attitudes such as stoicism and cautiousness in underreporting pain symptoms (Yong, 2006, Yong et al., 2001; Helme and Gibson, 2001). An alternative explanation that does not contrast with the previous one regards the general coping strategy adopted by elderly individuals in relation to life experience. Psychological theories (Lazarus et al., 1983) suggest that adults alter the priority over their life-span and consequently they appraise their experience differently. Thus, pain experience could be appraised differently in the elderly since pain is something to be expected as an aging factor and consequently is appraised as less intrusive whereas younger individuals will judge pain as a rare or an unexpected event and consequently as more intrusive (Yong et al., 2001). It has also been suggested that short duration stimulations such as CO_2-laser stimuli could accentuate age-related bias (Gibson et al., 1991). A study from Chakour et al. (1996) showed that response bias does not operate equally for A-delta and C-fiber nociceptive input. In particular, when reporting pain the elderly individuals would rely predominantly on C-fiber input whereas younger individuals will utilize additional input from A-delta fibers. The present study also utilized pressure stimulations of short duration (5sec.) whereas studies that investigate suprathreshold response of temporal summation stimuli (Edwards and Fillingim, 2001) and spatial summation (Lautenbacher et al., 2005) failed to observe response bias.

4.3 Gender-related age changes in pain thresholds and supra-thresholds

The present study showed significant lower pain detection and tolerance thresholds in young females as compared with young males. Instead, this difference is reduced to a non-significant level in the elderly. In addition, it was observed that pain detection threshold decreases as a function of age especially in men. On the contrary the tolerance threshold decreased as function of age in both males and females, although, this difference was visibly higher in the male group. The findings were consistent in all investigated body sites.

No significant interactions between age and gender were found at supra-threshold and sub-threshold ratings for both intensity and unpleasantness.

Both epidemiological (Unruh, 1996) and experimental (Fillingim and Maixner, 1995) studies have reported that females exhibit greater pain sensitivity and have higher prevalence of pain disorders than males. A number of individual studies and a meta-analysis (Riley et al., 1998) investigating gender difference in response to mechanically induced pain showed that females have lower pressure pain thresholds than males. This differential reporting of pain may be due to several factors such as biological, hormonal, genetic but also psychological, social and cultural. However, age and individual's past history might also play an important role in reducing these differences.

At the present, little is known about the interaction of gender and age changes in the perception of experimental pain. A study from Pickering et al. (2002) found that females both young and elderly have pressure nociception thresholds lower than males. However, when considering the age as factor pressure detection and tolerance

thresholds decreased especially in males. The data are in agreement with the present study where a reduction of pressure pain detection and tolerance thresholds was observed in males. However, another study from Lautenbacher et al. (2005) failed to detect any interaction between sex and age. The authors attributed the lack of difference to a small experimental sample employed.

4.4 Conclusions

These data suggest that assessment of pain in elderly should include suprathreshold and psychological factors in future investigations that might help to explain the complicated nature of the mechanisms.

The present findings indicate that the experience of pain in the elderly may differ from the experience in younger populations on multiple dimensions (sensory, affective and cognitive). Thus, elderly might require a greater coverage of pain-management strategies.

Investigating pain in the elderly population becomes increasingly important as due to the aging population in the western world. Hence more elderly citizens may suffer unnecessary pain.

Conflict of interest

The authors report no conflicts of interest in this work.

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Legend:

Figure 1. Pressure Pain Detection Threshold (PDT).

Figure 2. Pressure Pain Tolerance Threshold (PPTolT) .

Figures 3a-b. Supra and sub-thresholds self-reports (NRS): Pain and No-pain Intensities.

Figures 4a-b. Supra and sub-thresholds self-reports (NRS): Pain and No-pain Unpleasantness.

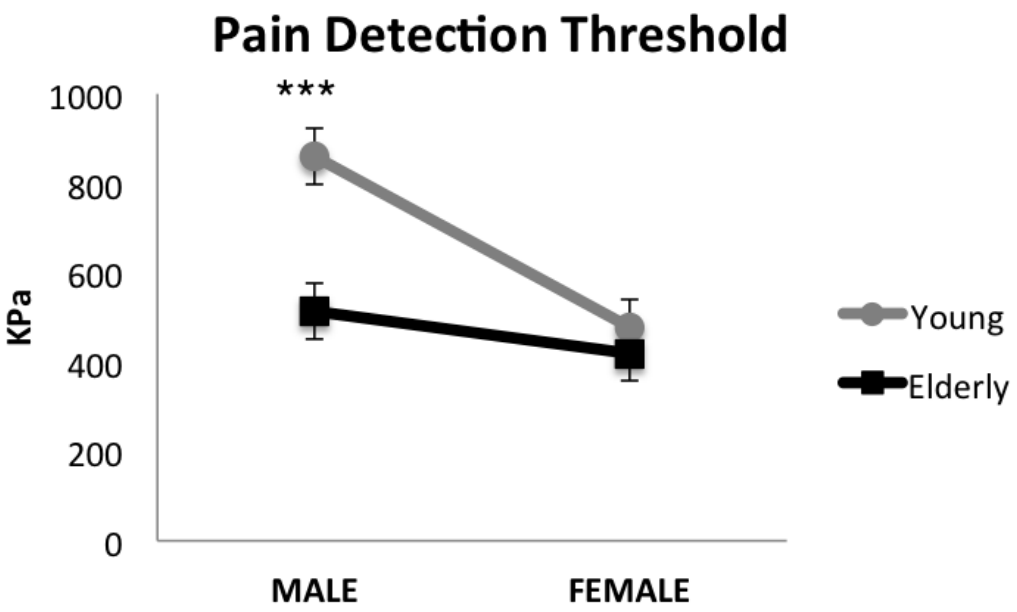


Figure 1. Pressure Pain Detection Thresholds (PDT).

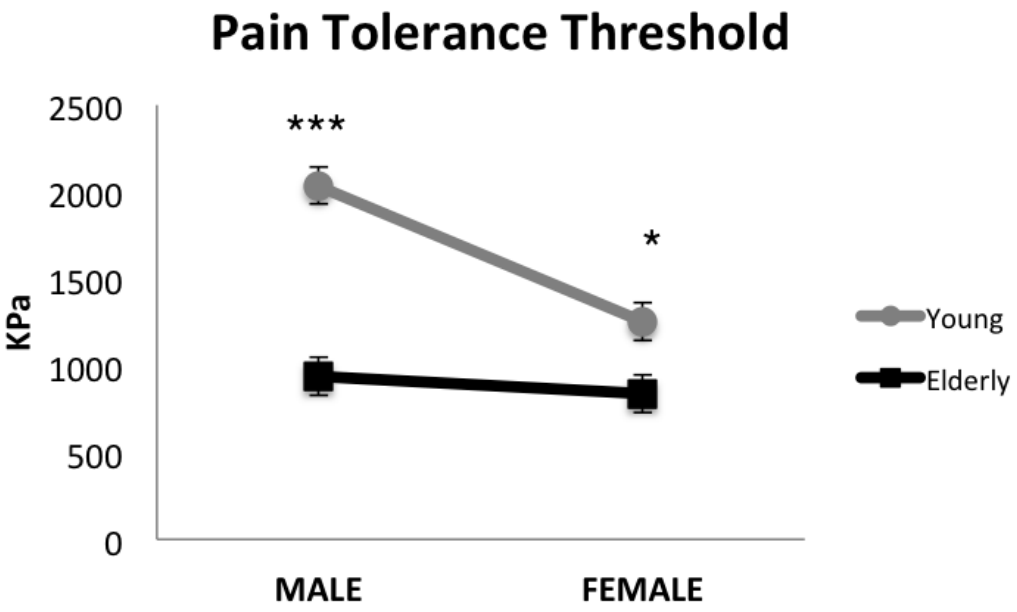
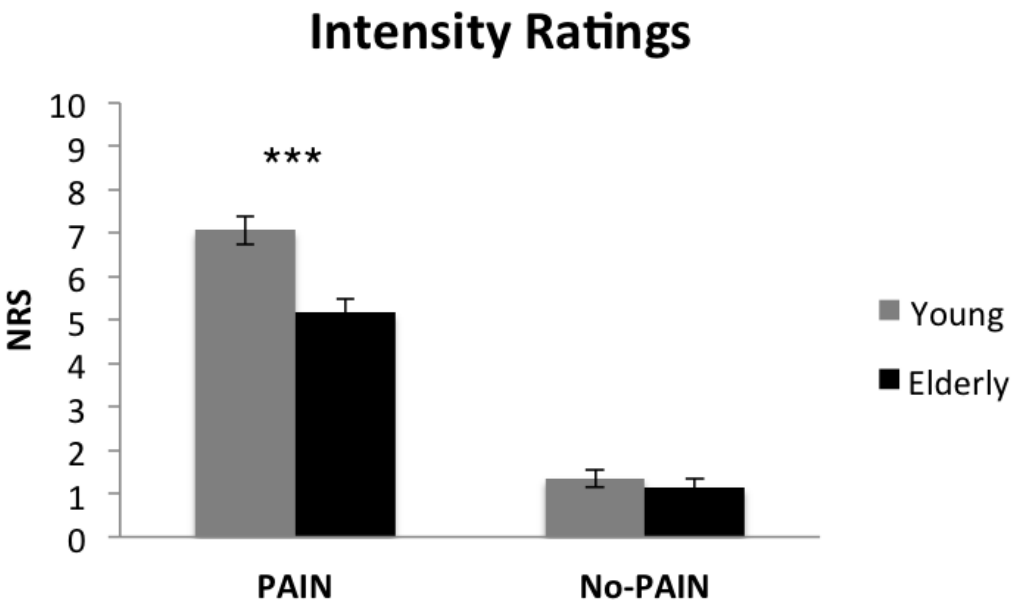


Figure 2. Pressure Pain Tolerance Threshold (PPTolT).



Figures 3. Supra and sub-thresholds self-reports (NRS): Pain and No-pain Intensities.

Figures 4. Supra and sub-thresholds self-reports (NRS): Pain and No-pain Unpleasantness.