Title: Intact pain modulation through manipulation of controllability and expectations in aging

Running head: Cognitive pain modulation in older adults

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Original article

Significance: This research describes the impact of age on cognitive pain modulation evoked by the manipulation of pain controllability and pain expectations. Our findings constitute a first step in the understanding of the greater vulnerability of older individuals to chronic pain. Moreover, we show that older adults can benefit from cognitive pain control mechanisms to increase the efficacy of pain treatments.

Abstract

Background: Pain expectation and controllability can modulate pain processing. However, little is known about age-related effects on these cognitive factors involved in pain control. This study assessed age-related brain changes associated with pain expectation and controllability. Methods: 17 healthy older adults (9 men; 65.65±4.34 years) and 18 healthy younger adults (8 men; 20.56±5.56 years) participated in the study. Pain evoked potentials and pain ratings were recorded while participants received painful electrical stimuli under two different conditions of pain controllability over the intensity of the stimulation (self-controlled vs. computer controlled) and two conditions of pain expectations (high vs. low pain). Results: Although the intensity of the painful stimulation was kept constant, all participants showed reduced pain perception in the controllable and low pain expectancy conditions. However, older participants showed reduced amplitudes of pain evoked potentials in the time window between 150 and 500 ms after stimulus onset as compared to younger participants. Moreover, younger participants showed greater negative amplitudes from 80 to 150 ms after stimulus onset for uncontrollable vs. controllable pain. Conclusions: These results suggest that although cognitive pain modulation is preserved during aging, neural processing of pain is reduced in older adults.

Keywords: pain, aging, cognitive modulation, controllability, expectations, electroencephalography.

1. <u>Introduction</u>

The interaction between cognition and pain has received vast attention from the scientific community, due to its potential impact on pain treatment (Seminowicz and Davis, 2007). As the population ages, emerge a crucial need of improving our understanding of the neurophysiological bases of pain and to investigate how cognition might modulate pain in aging. However, current research of age-related effects on pain modulation is scarce and available findings are inconclusive (Lautenbacher et al., 2017). Thus, for instance, it has been shown that distraction may worsen pain perception (Zhou et al., 2015a), and that pain inhibition was reduced in older compared to younger adults (Lithfous et al., 2019; Marouf et al., 2014). By contrast, some studies have revealed that both placebo (Wrobel et al., 2016) and distraction-induced analgesia (González-Roldán et al., 2020a) are preserved in aging. Furthermore, it has been observed that older adults displayed increased connectivity of pain-related sensory brain regions, and decreased connectivity of descending pain modulatory regions in comparison to younger participants (González-Roldán et al., 2020b). Thus, it has been proposed that aging might dull pain sensitivity leading to a delayed detection of external threats (Lautenbacher et al., 2017), but it might also deteriorate those brain mechanisms involved in the descending inhibitory control and in the processing of the salience or affective component of pain (González-Roldán et al., 2020b, 2020a).

In the present study, we assess age-related differences in two cognitive factors involved in pain processing and modulation: expectations and controllability. Expectations and

perceived control constitute relevant mediators to determine the impact of an aversive stimulus, such as pain (Fields, 2018; Woo et al., 2017). Indeed, cue-evoked expectations can bias pain perception by changing sensory processing and its emotional appraisal (Wiech, 2016), and the belief of having control over pain can reduce state anxiety, even when this control is illusory (Wiech et al., 2006, 2008). Regarding brain correlates of this modulation, it seems that cingulate and dorsolateral prefrontal cortices (dlPFC) would modulate pain expectation (Wiech et al., 2008), whereas brainstem regions as well as ventrolateral and ventromedial prefrontal cortices (vmPFC) would be involved in modulating pain responses based on perception of control (Salomons et al., 2014). Therefore, research of these mechanisms may contribute to our understanding of possible age-related abnormalities in pain processing and release. Furthermore, given that atrophy is particularly prevalent in these brain regions in the elderly (Farrell, 2012), it could be possible that pain modulation driven by expectations and perceived control are affected during aging.

Therefore, in this research pain-evoked event related potentials (ERPs) were recorded while participants received painful electrical stimuli under two conditions of pain control over the intensity of the stimulation (self-controlled vs. computer controlled) and two conditions of pain expectations (high vs. low pain). According to previous literature showing prefrontal atrophy in aging (Farrell, 2012; Maillet and Rajah, 2013), we hypothesized that, compared to younger adults, older adults will show a lesser reduction in perception of pain, along with increased ERP amplitudes, when pain is self-controlled and pain expectations are low.

2. <u>Methods and materials</u>

2.1. Participants

Participants were recruited from the University of the Balearic Islands (the older group was recruited from a senior academic program of the University). The sample was composed of 17 healthy older adults (9 men; 65.65±4.34, age range of 60-77 years) and 18 healthy younger adults (8 men; 20.56±5.56, age range of 18-26 years).

Prior to the day of the electroencephalographical (EEG) recording session, all participants underwent an initial semi-structured interview about their medical and psychological history. Persons presenting any psychiatric or neurological condition, acute or chronic pain, history of drug abuse, cognitive impairment (Mini Mental State Examination <27, (Lobo et al., 1999)) or left-handedness, were excluded from the study. All participants completed the Spanish versions of the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001), the Generalised Anxiety Disorder Assessment (GAD-7) questionnaire (Garcia-Campayo et al., 2010) and the Edinburgh Handedness Inventory (Oldfield, 1971). On the same day of the EEG recording, the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) was filled out to assess participants' mood at laboratory arrival. Finally, after the EEG experiment was carried out, all participants completed the Spanish versions of the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), the Rotter's Locus of Control Scale (LCS) (Perez-Garcia, 1984) and The Brief Cope Inventory (COPE) (Carver, 1997). *Table 1* displays clinical and sociodemographic data of both groups. Group comparisons for GAD-7, catastrophizing (PCS) and locus of control (Rotter's LCS) scores showed no differences (see *Table 1*). Concerning the COPE, older participants scored higher in the active coping, use of religion and positive reframing subscales and lower in the substance use subscale (all p<.05) in comparison to younger

participants. Moreover, older participants showed higher scores than young in the PHQ-9 and the PANAS positive subscale (p<.05).

All individuals were naive to the experiment and gave written informed consent prior to participating. The study was conducted in accordance with the Declaration of Helsinki (1991) and was approved by the Ethics Committee of the Balearic Islands.

---- Insert Table 1 about here-----------

2.2. Painful stimulation

Electrical pain stimuli were delivered using a DS7A Digitimer (Digitimer Limited - United Kingdom). Stimulation was applied to the ventral side of the non-dominant wrist (left) using a modified version of the electrode described by Inui and colleagues (Inui et al., 2002). The intensity of pain stimulation during the experiment was adjusted for each participant to elicit a pain rating equal to 5 in a numerical rating scale. In detail, participants were instructed to rate equal to 0 if the stimulus was not perceived, equal to 1 if stimulus was detected but it was considered non-painful ("no pain, just electrical sensation", sensory threshold), equal to 2 when the stimulus was perceived as painful (i.e. pain threshold) and equal to 10 for the worst pain imaginable. Therefore, in the experiment we used a mild painful stimulation equal to 5 in a scale ranging from 1=no pain to 10=maximum pain imaginable (equal to 4 in a 0 to 10 scale). The method of limits (Boivie et al., 1989) was used to determine individual sensory threshold, pain threshold and mild pain perception. According to this method, participants received three ascending series of electrical pulses and the mean of the two last series was computed. In each series, we first determined the sensory threshold by presenting 1 ms stimuli ranging from a

baseline of 0 increasing in steps of 0.05 mA, with 5 s Inter-Stimulus Interval (ISI). After reaching sensory thresholds, we increased the stimulation in steps of 0.25 mA, with 8 s ISI, until a maximum of 5.5 mA. After each stimulus, subjects rated the pain intensity felt.

2.3. Experimental design

We adapted a validated fMRI paradigm developed to manipulate the feeling of control over pain and pain expectations (González-Roldán et al., 2016). In this task, participants were told that they would participate in a reaction time experiment and that they could reduce the intensity of painful stimuli depending on their performance. In the control condition, participants saw an image of a right hand with one of the five fingers coloured in yellow (see Fig. 1 for the study design). The task of the subject was to respond as quickly as possible with the indicated finger of their right hand on a response pad with five buttons (one for each finger). Participants received visual feedback based on their behavioural performance: if the response was fast enough, a smiling face was shown on a green background, indicating that the intensity of the subsequent pain stimulus would be of lower intensity. Such a trial corresponded to the control condition and low pain expectation, "Control/Low Expectation". By contrast, if the response was too slow, a sad face was shown on a red background, indicating that the following stimulation would be of higher intensity ("Control/High Expectation"). In the uncontrollable pain conditions, participants were told that they would have no control over the intensity of the pain stimuli. These trials were indicated by the presentation of a picture of a right hand with no coloured fingers. Participants were told to just press any button to continue with the task. They were then presented with a circle either on a green background ("No-

Control/Low Expectation") or on a red background ("No-Control/High Expectation"), indicating a reduced or increased intensity of the subsequent electrical stimulus, respectively. After the button press, the predictive feedback was presented during 5 s and followed by a 1 s fixation cross. After this period, participants received a painful electrical stimulus to the inner left wrist. Regardless of the instruction and unknown to the participant, the intensity of the pain stimuli was kept constant for all conditions. After the painful stimulation, participants rated the intensity and unpleasantness of the painful stimuli on computerised visual analogue scales (VAS) ranging from no pain/not unpleasant to worst pain imaginable/highly unpleasant (0- to 100-mm long scale). After the ratings, a 3 s fixation cross was presented. For all participants, 32 controllable trials (16 with low pain expectation and 16 with high pain expectation) and 32 uncontrollable trials (16 low pain expectation and 16 high pain expectation) were presented in pseudorandom order, avoiding that the same condition appeared more than twice. To maintain the illusion of control, participants automatically received negative feedback (i.e., the sad face on a red background) if they responded with an incorrect finger or the button was not pressed. Before the experiment, all participants performed a few practice trials to get familiar with the task instructions, to learn how to use the response pad and to rate the pain stimuli using the computerized VAS.

--Insert Figure 1 about here----

2.4. EEG data processing

EEG signals were recorded using a QuickAmp amplifier (BrainProducts GmbH, Munich, Germany) from 60 scalp electrodes placed according to the international 10/20 system. Electrode signals were recorded using an average reference calculated by the amplifier. An electrooculogram (EOG) channel was obtained by placing one electrode above and another below the left eye. Electrode impedance was kept below 10 KΩ. EEG and EOG signals were recorded with a sampling rate of 1,000 Hz using BrainVision Recorder software (BrainProducts GmbH, Munich, Germany).

EEG signals were further processed off-line with Matlab R2018b, using the EEGLAB toolbox 14.1.2 (Delorme and Makeig, 2004). First, we applied a band-pass filter of 0.5-30Hz. Then, EEG data were segmented in epochs of 1100 ms duration (-100 ms to 1000 ms relative to the painful stimulus onset) and baseline corrected (from -100 ms to 0 ms). Eye movement and electrical pulse artefacts (from electrical painful stimulation) were identified using an Independent Component Analysis and manually removed. Finally, an automatic epoch rejection protocol was used to remove epochs containing activity higher than $120\,\mu V$ at any channel. All participants met the inclusion criterion of keeping at least 70% of trials free of artefacts for each of the four conditions.

EEG data analysis was then performed in two steps. First, we conducted a non-parametric cluster-based permutation test (CBPT). Mass univariate analyses, such as CBPT, are becoming important in building a more reliable and replicable ERPs literature (Fields and Kuperberg, 2020). This method allows for testing group or condition differences in high-dimensional neural data while taking into account the multiple comparisons problem (Maris and Oostenveld, 2007). However, caution must be taken when making inferences about the effect of latency or location with CBPT (Sassenhagen and Draschkow, 2019)

and, therefore, the exact latency values and electrode locations should be treated as approximate. Moreover, permutation-based corrections of CBPT support only single factor designs and do not constitute the best method for complex paradigms as ours (2x2x2 design) (Fields and Kuperberg, 2020). Therefore, we first used CBPT to detect the temporal windows and electrodes showing significant differences between groups and then tested potential interaction effects between conditions (controllability vs. expectation) and groups by using the usual spatiotemporal averaging approach. CBPT analyses were performed over 42 electrodes and a time window ranging from 0 to 500 ms after the painful stimulus onset by using the Fieldtrip toolbox (Oostenveld et al., 2011). For every sample (electrode x millisecond), groups (older and younger) were compared in each of the four conditions (Control/High Expectation, Control/Low Expectation, No-Control/High Expectation, No-Control/Low Expectation) by means of an independent sample t-test. All conditions were also compared for each group separately by means of a dependent sample t-test. Those samples whose t-values were higher than the critical level (p < .05) were selected and clustered by temporal and spatial adjacency. Next, t-values within every cluster were summed to calculate the cluster-level statistics. These observed cluster-level statistics were evaluated through a non-parametric permutation test. The permutations were created by randomly assigning labels and running the test 1000 times, retrieving the maximum cluster statistic every time. Only if the observed cluster-level statistics from the real data were larger than 95% of the maximum cluster statistics in the permutation distribution (Monte Carlo significance probability), the observed effects were considered as statistically significant. In agreement with previous literature about pain ERPs (Özgül et al., 2017), significant differences between groups were located around the vertex, and in time windows matching with the known N1, P1

and P3 ERPs (see supplementary material and Figure 3). Thus, in a second step, peak-to-peak N1-P1 and P3 amplitudes were examined by performing a temporal averaging in electrodes located around the vertex (C3, Cz and C4) on the following time windows: 80-150 ms for N1, 150-200 ms for P1, and 200-350 ms for P3.

2.5. Statistical analyses

To test the effects of controllability and expectations on pain perception in older and younger adults, subjective pain ratings (intensity and valence) and EEG data were separately analysed with repeated-measures ANOVAs. Pain intensity and pain unpleasantness ratings were analysed with repeated-measures ANOVA with *group* (older vs. younger) as the between-subjects factor and *control* (Control vs. No-control), *pain expectation* (Low vs. High) and scale (intensity and unpleasantness) as within-subject factors. Peak-to-peak N1-P1 and P3 amplitudes were separately examined by using repeated-measures ANOVA with the following factors: *group* (older vs. younger), *control* (Control vs. No-control), *pain expectation* (Low vs. High) and *laterality* (left (C3), midline (Cz), right (C4)). Degrees of freedom were corrected using the Greenhouse–Geisser epsilon correction and post-hoc pairwise mean comparisons were also Bonferroni corrected.

Finally, questionnaire scores and demographic data were analysed with independent sample t-tests for group differences. Given that previous research has shown that hypertension can change pain thresholds (Saccò et al., 2013), differences between groups in sensory and pain thresholds, as well as, in the mild painful stimulation intensity were analysed with an ANOVA using the presence of hypertension as covariate (6 older participants were diagnosed with hypertension).

3. Results

3.1. Pain thresholds and pain ratings

There were no group differences in sensory or pain thresholds to electrical stimulation, neither in the mild painful stimulation intensity used, and hypertension did not influence these results (all ps >.05, see Table 1).

Repeated measures ANOVA of pain intensity and unpleasantness ratings showed a significant main effect of *control* ($F_{(1,33)}$ = 6.296, p=.032, η_p^2=0.132) and *pain expectation* ($F_{(1,33)}$ = 18.536, p<.001, η_p^2=0.399, see Fig. 2). Pain stimuli in the "High pain expectation" conditions were evaluated as more intense and unpleasant than those in the "Low pain expectation" conditions (regardless of the controllability level). Likewise, stimuli in the "No-Control" conditions were rated as more intense and unpleasant than those in the "Control" conditions (regardless of the pain expectation condition). No significant main effects or interactions regarding *group* were found.

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3.2. EEG results

The CBPT revealed that there was a significant difference between older and younger groups in the four conditions that extended from 140 to 500 ms approximately (see Fig. 3 and supplementary material for more details). In all conditions, the painful event related activity was significantly lower in the older group when compared to the younger group.

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According to CBPT results, repeated measures ANOVAs analyses of ERPs showed significant main effects of *group* on N1-P1 (($F(1,33)=13.873$, p=.001, $\eta_p^2=0.296$) and P3 ($F(1,33)=16.415$, p<.001, $\eta_p^2=0.332$), showing that older adults displayed lower amplitudes than younger participants. A significant *laterality* x *group* ($F(2,66)=7.809$, p=.002, $\eta_p^2=0.191$) interaction on N1-P1 specified that N1-P1 amplitudes were larger in younger participants in comparison to older participants at Cz (p<.001) and C3 (p=.005). In addition, younger participants showed larger N1-P1 amplitudes in Cz than in C3 (p<.001) and C4 electrodes (p=.011), while no differences between electrodes were found in older participants. Finally, we found a significant main effect of *control* ($F(1,33)=5.704$, p=.023, $\eta_p^2=0.147$) on N1-P1, showing that perceived control over pain led to reduced N1-P1 amplitudes in comparison to having no perceived control (regardless of the pain expectation condition). However, as can be seen in Figure 4 these differences were mainly observable in younger adults. No differences between conditions were found in P3 (see Fig.5). No significant interactions between *group*, *pain expectation* and/or *pain control* were found.

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4. Discussion

The present study investigated, for first time, pain ratings and pain ERPs during the manipulation of perceived control and expectations about the intensity of pain in younger and older healthy adults. We found that pain was reduced in older participants to the same

14

degree as in younger participants, under conditions of low pain expectation and perceived control over the stimulation intensity. Indeed, although the intensity of the painful stimulation was kept constant, all participants rated the stimuli as more painful during the uncontrollable than during the controllable condition. On the other hand, the stimuli were rated as more painful and unpleasant during the high pain expectation condition than during the low expectation condition. Therefore, both younger and older participants showed the expected effects of the experimental manipulation, which suggests that cognitive modulation over pain is preserved in healthy older individuals. This result is in agreement with a previous study in which we employed a pain distraction paradigm (González-Roldán et al., 2020a), as well as with studies showing a significant placebo effect among older participants in a pain paradigm (Wrobel et al., 2016), in clinical trials of antidepressants and in treatments of Parkinson's disease (see Cherniack, 2010 for a review). However, our results contrast with other studies showing reduced pain inhibition in older compared to younger adults in distraction paradigms and during conditioned pain modulation (Lithfous et al., 2019; Marouf et al., 2014; Zhou et al., 2015a, 2015b). At least two explanations might account for these differences. First, discrepancies in the results could be related to differences in the sample characteristics. Indeed, Zhou et al. (2015a, 2015b) argued that disturbance in cognitive modulation of pain perception in older adults could be related to reduced functioning of frontal networks. Our sample was composed of 17 healthy and cognitively active adults (engaged in a University Senior Program). Therefore, variability in cognitive status of older participants may, to some degree, have contributed to the contradictory findings regarding cognitive pain modulation in aging. Another explanation is that the different paradigms used to assess cognitive pain modulation have different underlying neurobiological mechanisms (Wrobel et al., 2016).

It has been shown that pain modulation relies on the dlPFC-ACC axis, which is involved in higher-order regulation processes, but also on limbic-affective brain regions (Roy et al., 2015; Wiech et al., 2008). In contrast to the dlPFC, which is strongly affected by aging, the structure and function of the amygdala and the vmPFC, key regions of the emotion-related circuitry, show relatively little decline in aging (Mather, 2016). This fits with the observation of a preserved or even enhanced modulation of attention through expectations or cues with an affective component in healthy older adults (Madden, 2007) (an ability that relies on vmPFC) (Brassen et al., 2011, 2012; Mather, 2016). The vmPFC also appears to be critically involved in modulating pain responses based on the perception of control (Salomons et al., 2014). Therefore, as Wrobel et al. (2016) pointed out, the vmPFC may compensate for a decline in functioning of the dlPFC in paradigms involving the modulation of pain expectations and pain controllability. Our data do not allow to discern, however, if the contrasting findings are the result of naturally occurring variability in the aging process, or of methodological differences leading to the recruitment of divergent neurobiological mechanisms, or both. It is also not clear if our results are generalizable to older adults with poorer cognitive functioning or older adults suffering from chronic pain. This latter is an important question, given that more than 50% of the elderly population has chronic pain disorders (Helme and Gibson, 2001). In the light of our aging society, further efforts to answer these questions are crucial.

We found that older participants showed a generalized reduction of pain ERP amplitudes in comparison to younger participants in a time window ranging from 150 ms to 500 ms across all experimental conditions. This result is in agreement with our previous study (González-Roldán et al., 2020a), as well as with others using electrical (Özgül et al., 2017), laser (Creac'H et al., 2015; Gibson et al., 2001; Gibson and Farrell, 2004) and heat

stimulation (Chao et al., 2007). Therefore, this global age-related reduction in pain ERP amplitudes, seems to be a robust finding which it is not affected by experimental manipulations, such as those changing pain controllability, expectations, or attention (González-Roldán et al., 2020a). Indeed, as can be seen in figure 5, younger participants showed the reduced peak-to-peak N1-P1 amplitudes expected for controllable vs. uncontrollable pain (Hird et al., 2018; Perchet et al., 2008; Rütgen et al., 2015). Despite older adults reported a similar pain relief to younger adults during the controllable condition, this ERP modulation was almost absent in this group. In our opinion there are two non-mutually exclusive explanations for this lack of congruence between modulation of pain ratings and brain activity in the older group: first, it is possible that due to the flattening of the ERPs in the elderly, this modulation was not observable. Second, considering that N1-P1 is related to the encoding of pain salience in a specific context (see Legrain et al., 2012 for a review), our results could indicate that the early coding of stimulus salience of pain is altered in the older population. This interpretation is in agreement with previous studies suggesting that aging lead to a delayed detection of external threats, such as pain (Lautenbacher et al., 2017), perhaps by deterioring the brain mechanisms involved in the processing of the salience or affective component of pain (González-Roldán et al., 2020b, 2020a). Further studies should replicate our findings with more sensitive measures of brain activity to fully answer these questions.

There are some aspects of the present research that merit further consideration. We used a combination of CBPT and temporal averaging to analyze EEG data. The use of mass univariate techniques increases the reliability of the results (Fields and Kuperberg, 2020). In addition, both behavioral and ERP data showed effective modulation by expectations and feelings of control, thus validating our paradigm. However, the two samples are

small and quite homogeneous, which limits the generalizability of our results. Nevertheless, this also highlights one of the main strengths of the study, namely the demonstration that aging leads to alterations in pain processing even in healthy and active older adults. However, more studies should be performed with larger sample sizes and considering other potential factors that could influence the effects of aging on pain perception (for instance sex of the participant), in order to extend and further validate our results.

In conclusion, our results demonstrates that neural responses to pain are reduced in older adults. This alteration could be the starting point of the changes leading to the greater vulnerability of older individuals to chronic pain disorders. However, and more importantly, our study shows that the capacity to inhibit pain through adjusting expectations and the perception of control is preserved in the older population. This could be capitalized on by medical practitioners, since conventional interventions in older adults are limited due to possible comorbidities and pharmacological interactions (Farrell, 2012). It is well known that empowering the patient (e.g. giving additional medical information and encouraging active input to the treatment approach), as well as creating positive expectations about the efficacy of a given treatment, increase its effectiveness (Wiech, 2016; Younger et al., 2008). Our study confirms that older adults can still benefit from these endogenous mechanisms of pain control to increase the efficacy of pain treatments.

Author Contributions

All authors discussed the results and commented on the manuscript. AG and MP discussed the original design of the experiment. AG and MP acquired the data. AG and JT analyzed the data. AG, JT, MP, CS, FA, MvM, and PM revised the manuscript.

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Figure legends

Fig. 1. Timeline of the stimulation protocol. In "Control" trials a picture of a right hand with a yellow-coloured finger was presented, and participants pressed a response button as quickly as possible using the finger indicated. This was followed by the presentation of feedback in the form of a green smiley or red sad face, the painful electrical stimulation, a rating phase during which participants indicated perceived pain intensity and unpleasantness on VAS scales, and lastly by an inter-trial interval. In "No-Control" trials the same hand picture was presented but without the yellow finger.

Fig. 2. Ratings for pain intensity and pain unpleasantness. Means and standard errors of means for pain intensity (left panel) and pain unpleasantness ratings (right panel) for older and younger participants in each condition. Pain intensity and unpleasantness ratings were higher for the high pain expectation conditions than for the low expectation conditions,

as well as, for the "No-control" conditions than for the "Control" conditions, in both groups.

Fig. 3. Brain topography of the significant differences between groups in the pain-related evoked potential in the "Control/ High Expectation", "Control/ Low Expectation", "No-Control/ High Expectation" and "No-Control/ Low Expectation" conditions. Three representative time points are shown. Asterisks indicate the electrodes showing significant differences at each time point. Blue colour indicates reduced amplitudes in the older group compared to the younger one.

Fig. 4. Grand averages of pain ERPs elicited in the "Control/ High Expectation", "Control/ Low Expectation", "No-Control/ High Expectation" and "No-Control/ Low Expectation" conditions at central electrodes (Cz, C3 and C4) for younger (black lines) and older (grey lines) participants.

Fig. 5. Grand averages of pain ERPs elicited in each group by the four conditions ("Control/ High Expectation", "Control/ Low Expectation", "No-Control/ High Expectation" and "No-Control/ Low Expectation") at the Cz electrode.