The effect of unpredictability on the perception of pain: A systematic review and meta-analysis

Fabien Pavy[1], Jonas Zaman[1,2,4], Wim Van den Noortgate[3], Aurelia Scarpa[1], Andreas von Leupoldt[1], Diana M. Torta[1]

[1] Research Group Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Belgium

[2] Centre for the Psychology of Learning and Experimental Psychopathology, Faculty of Psychology and Educational Sciences, KU Leuven, Belgium

[3] Methodology of Educational Sciences, Faculty of Psychology and Educational Sciences, & itec, an imec research group, KU Leuven, Belgium

[4] School of Social Sciences, Hasselt University, Belgium

Data availability statement:

Datasets and analysis codes can be found on the Open Science Framework (https://osf.io/qkwr7).

Corresponding author:

Diana Torta

Mail: Health Psychology, Tiensestraat 102, box 3726, 3000 Leuven, Belgium

Email: diana.torta@kuleuven.be

Phone number: +32 16 37 66 23

URL of institution: https://ppw.kuleuven.be/ogp

Abstract

Despite being widely assumed, the worsening impact of unpredictability on pain perception remains unclear due to conflicting empirical evidence, and a lack of systematic integration of past research findings. To fill this gap, we conducted a systematic review and meta-analysis focusing on the effect of unpredictability on pain perception. We also conducted meta-regression analyses to examine the moderating effect of several moderators associated with pain and unpredictability: stimulus duration, calibrated stimulus pain intensity, pain intensity expectation, controllability, anticipation delay, state and trait negative affectivity, sex/gender and age of the participants, type of unpredictability (intensity, onset, duration, location) and method of pain induction (thermal, electrical, mechanical pressure, mechanical distention). We included 73 experimental studies with adult volunteers manipulating the (un)predictability of painful stimuli and measuring perceived pain intensity and pain unpleasantness in predictable and unpredictable contexts. As there are insufficient studies with patients, we focused on healthy volunteers. Our results did not reveal any effect of unpredictability on pain perception. However, several significant moderators were found, i.e. targeted stimulus pain intensity, expected pain intensity and state negative affectivity. Trait negative affectivity and uncontrollability showed no significant effect, presumably due to the low number of included studies. Thus, further investigation is necessary to clearly determine their role in unpredictable pain perception.

Introduction

Around 19% of the European adult population suffers from moderate to severe chronic pain [87] and a common belief attributes to unpredictability a role in pain magnification. Unpredictability of pain can be defined as the quality of having no or inconsistent information [86] about pain episodes (e.g., about their onset, intensity, duration, location). For patients with chronic pain, this may lead to highly distressing impairments of autonomy and well-being [19,133]. However, the role of unpredictability is not clear-cut, especially in healthy volunteers. While some experimental studies confirm that unpredictable painful stimuli result in higher perceived intensity than predictable ones [6,8,127], other studies report unpredictable painful stimuli being perceived as less or equally intense than predictable ones [13,83,84,91,110,129].

Experimental manipulations of unpredictability often unintendedly affect other variables [128], possibly leading to the aforementioned contradictions. First, predictable and unpredictable conditions can induce differences in expected pain intensity because humans do not remain naive throughout an experiment but acquire expectations based on their past pain experiences which may differ between conditions [128]. These differences in expectations may partly explain unpredictable pain perception [13,83,128]. Second, differences in controllability might emerge in unpredictability manipulations as predictability facilitates controllability [73]. In previous experiments, controllability was found to alleviate pain suffering [65] and to reduce pain ratings [65,78], although not always [12,78]. Third, unpredictable pain may increase fear and anxiety (transiently, we will refer to this as state affects) [31], which in turn have been proposed to modulate pain perception but sometimes in different directions [69,92]. Fear and anxiety may also depend on anticipation delays and their predictability [31,36]. Yet, the effects of unpredictable anticipation delays on pain have not been consistently found [8,15,18,20].

Individual characteristics can also concur to modulate pain, although the interplay between these variables and unpredictability is not fully elucidated. For instance, fear of pain and anxiety [64,67,108], higher age [59] and female sex/gender [21,22,25,71,93,99] have been associated with elevated pain. One study examined unpredictability and sex/gender-specific effects on pain perception, but could not provide definitive answers [71]. No other study focusing specifically on the effects of these individual characteristics on unpredictable pain perception could be identified. Yet these characteristics are often reported in manuscripts, thus enabling meta-analytical attempts to investigate their possible effects on unpredictable pain perception.

A systematic integration of evidence about the effects of unpredictability on pain perception is currently lacking. Here, we aim to fill this gap by conducting a systematic review and meta-analysis on the effects of unpredictability on perceived pain intensity and unpleasantness, as well as by testing the role of potential moderators. We searched the literature for experimental studies in adult volunteers manipulating the unpredictability of painful stimuli and measuring ratings of pain intensity and pain unpleasantness in (un)predictable conditions. We also conducted a series of meta-regression and random

forest analyses to examine the effects of potential moderators: targeted stimulus pain intensity, stimulus duration, expected pain intensity, controllability, state and trait negative affectivity, age, sex/gender, method of pain induction (thermal, electrical, mechanical pressure and mechanical distention), type of unpredictability (onset, intensity, duration, location) and anticipation delay.

Method

Open Science Statement

The experiment and analyses have been pre-registered at the Open Science Framework (https://osf.io/qkwr7) where the original dataset (pre-imputation), analysis code and supplementary material can also be found.

Eligibility criteria

Recruited participants had to be older than 18 years. If a study reported the effects of multiple age groups, only the effect sizes for the age groups older than 18 years were included. Studies with healthy volunteers or with patients with chronic pain, i.e. a persistent or recurrent pain lasting for more than 3 months [111] were both eligible.

We defined unpredictability based on Pervin's definition [86]: the instance of having no or inconsistent information regarding an event. To be included, a study needed to contain a manipulation of unpredictability with one condition being more unpredictable than another. Experiments manipulating unpredictability through cues or verbal suggestions were both eligible. Unpredictability could refer to the stimulus onset, intensity, duration, and location (see taxonomy in Table 1).

We only included studies where at least one predictable and unpredictable stimulus was evaluated as painful or was around the pain threshold. We accepted three types of outcomes: pain intensity ratings, pain unpleasantness ratings, and ratings of pain threshold (subsequently grouped in the analyses with pain intensity ratings). These ratings had to relate specifically to the predictable and unpredictable conditions, and be reported separately for each condition. Studies which failed to meet this requirement [28,131] were excluded and reported under the category "no (usable) pain ratings in the predictable and unpredictable condition" (see flowchart in Figure 1). Moreover, to justify study inclusion, the predictable and unpredictable conditions had to contain stimuli of matched intensity and duration, administered in a similar manner, with the same device and in the same environment (e.g. both inside or outside a scanner).

Eligible articles needed to provide original data and to be in English language, either published or in press at the moment of the literature screening. We decided to not include unpublished studies as

they were more difficult to identify and not peer-reviewed. Verifications were made prior to the analyses to ensure that this did not lead to any publication bias (supplementary materials, Figure S1).

Literature screening and study selection

We based our work on the guidelines of the Cochrane handbook for meta-analyses [37] and of PRISMA (http://www.prisma-statement.org/). Two researchers (FP, AS) performed the literature screening and proceeded in several stages. In the first stage, they searched the PubMed and PsycInfo databases (November 2020) for relevant articles. Search strings comprised the terms: "pain AND unpredict* NOT animal NOT review"; "nocicept* AND unpredict* NOT animal NOT review"; "noxious AND unpredict* NOT animal NOT review"; "pain AND uncertainty NOT animal NOT review"; "nocicept* AND uncertainty NOT animal NOT review"; "noxious AND uncertainty NOT animal NOT review". As described in Figure 1, we retrieved 2 501 unique abstracts on PubMed and PsycInfo. Based solely on the evaluation of the abstracts, 2 426 ineligible studies were excluded. The full text of the remaining 75 studies was evaluated by two researchers (FP, AS) who worked independently and compared their evaluations afterwards. In case of disagreement, a third party (JZ, AvL or DT) was consulted. This stage ended with the selection of 34 relevant articles.

In the second stage, the two evaluators completed the literature screening with several rounds of backward and forward snowballing in Google Scholar [121] (from February to May 2021) until no new eligible study could be found. Backward snowballing consists in retrieving relevant studies in the references of the already included articles. In contrast, forward snowballing consists in retrieving relevant studies that cite the already included articles. The articles included after a round of forward and backward snowballing are typically used to realize the next round, and this until no new study can be found. The retrieved studies in each round were broadly filtered by either evaluator. The remaining articles were then independently assessed by each researcher. Their decisions were compared as previously described. In total, 15 722 titles were screened out of which 868 studies were considered potentially eligible. The abstracts of these studies were evaluated and led to the screening of 309 full-text articles, resulting in the inclusion of 30 additional studies (see flowchart in Figure 1). An update of the forward snowballing method was conducted in January 2023. This time, a single researcher (FP) screened 1 521 titles, 55 abstracts and 21 full-texts. This update led to the additional inclusion of 3 studies for a total of 67 studies.

Risk of bias

The risk of bias of each effect size was assessed with the revised Cochrane risk-of-bias tool (ROB2 [38]). The absence of counterbalancing order between the predictable and unpredictable conditions and the manipulation of controllability (along with unpredictability) were added as complementary criteria leading to a high risk of bias assessments. Imputed effect sizes were systematically evaluated as being at high risk of bias. The risk of bias assessment was realized by a

single researcher (FP) who applied the commonly decided criteria. In case of doubt (< 10% of the effect sizes), the opinion of another co-author (JZ, AvL, DT) was asked and the final assessment resulted from a joint agreement.

Data extraction

We calculated Hedges' g effect sizes [9,58] representing the standard mean differences in ratings of pain intensity, pain threshold (grouped with pain intensity for the analyses) or pain unpleasantness between the predictable and unpredictable conditions, adjusted for the studies sample sizes. From now on, to remind to the reader that the difference between predictability and unpredictability is embedded in Hedges' g, we will refer to the effect sizes as Hedges' g (P-U). Hedges'g (P-U) took a negative sign when pain was rated as more intense or unpleasant in the unpredictable than in the predictable condition and a positive sign otherwise. All the metrics needed to calculate the effect sizes or their variance [9] were retrieved from the manuscripts, from the tables and figures or calculated with the datasets available online or provided by the authors of studies upon request.

We expected high heterogeneity in the study results [128], therefore we made use of random effects models and we planned meta-regression analyses to try to explain this heterogeneity. To conduct these meta-regressions, we extracted a series of variables: 1) ***Targeted stimulus pain intensity:*** Given the variability in the characteristics of stimulus intensities (e.g. electrical, thermal, mechanical pressure and distention) across studies, we decided to use as moderator the reported pain intensity targeted by the stimuli. This variable had the main purpose to determine whether the effects of unpredictability could vary between pain intensity levels (e.g. low, medium or high pain) as sometimes found in empirical studies [13]. Values for this variable were calculated by using the pain ratings during calibration, or when unavailable, by averaging the ratings across all experimental study conditions to get an estimate independent from any specific condition (that is not related specifically to predictability or unpredictability unlike our dependent variable Hedges'g (P-U), and not related to any specific level of our moderators). For the latter method, only pain ratings to identical stimulus intensities were averaged such that all averaged pain ratings and the resulting average estimate approximately represented the same level of pain intensity (see supplementary materials for examples and the discussion for more details). *Targeted stimulus pain intensity* was represented on a standardized 0-100 scale with for labels 0 = no pain, 1 = pain threshold, 80 = very strong pain, 100 = extreme/highest pain imaginable. 2) ***Differences in expected pain intensity (P-U)*****:** difference in expected pain intensity between the predictable and unpredictable conditions (negative difference: higher expected pain intensity in the unpredictable condition, positive difference: higher expected pain intensity in the predictable condition, scale range: -100, 100). Expected pain intensity was calculated as the average of the targeted stimulus pain intensities per condition such that expected pain intensities could differ between the predictable and unpredictable conditions whenever corresponding targeted stimulus pain intensities also differed.

(see supplementary material for more information). 3) ***Differences in anticipation delay (P-U)*** was calculated as the difference in anticipation delay between the predictable and unpredictable conditions. This difference could occur when the unpredictability of the pain onset was manipulated, with sometimes different anticipations in the compared predictable and unpredictable conditions (negative difference: longer anticipation in the unpredictable condition, positive difference: longer anticipation in the predictable condition, scale unit: seconds). 4) ***Method of pain induction***: electrical, thermal, mechanical pressure or mechanical distention. 5) ***Type of unpredictability***: onset, intensity, duration or location (see taxonomy in Table 1). 6) ***Stimulus duration*** (scale unit: seconds). 7) ***Age****:* average age of the sample (scale unit: years). 8) ***Sex/Gender****:* ratio of women in the sample. Sex and gender were not distinguished because of the overlap of the two concepts in most studies and because it was not always possible to determine with certainty whether authors asked for sex or gender identity in their questionnaires. 9) ***Trait negative affectivity:*** (scale: 0: minimum possible score; 100: maximum possible score). 10) ***Differences in trait negative affectivity (P-U)***: difference in trait negative affectivity between the predictable and unpredictable conditions (negative score: higher trait negative affectivity in the unpredictable condition, positive score: higher trait negative affectivity in the predictable condition, standardized scale range: -100, 100). For within design studies, these differences equaled zero. 11) ***Differences in state negative affectivity (P-U)***: difference in state negative affectivity between the predictable and the unpredictable conditions (negative score: higher state negative affectivity in the unpredictable condition, positive score: higher state negative affectivity in the predictable condition, standardized scale range: -100, 100). We made the choice of merging fear and anxiety scores under the concept of negative affectivity. Although a part of the literature has proposed that fear and anxiety have differential effects on pain perceptions [31,92], other studies have shown increased pain perception with both increased fear and anxiety [27,71,121] which motivated our decision to merge both emotions under the same construct (see *Discussion* for details).

For comparability purposes across studies, a few variables listed in the previous paragraph had to be standardized: *targeted stimulus pain intensity*, *trait negative affectivity* and *state negative affectivity*. More variables depended on these three variables and were consequently also standardized: *differences in expected intensity*, *differences in trait negative affectivity (P-U)* and *differences in state negative affectivity (P-U)*. All standardization processes are explained hereafter and concrete examples can be found in the supplementary materials. *Targeted stimulus pain intensity* needed to be standardized because different studies used different pain scales. It was standardized on a 0-100 scale with for labels 0 = no pain, 1 = pain threshold, 80 = very strong pain, 100 = extreme/highest pain imaginable. This was done with the formula: *(targeted pain rating – (scale pain threshold - 1)/(scale maximum – (scale pain threshold - 1))* x *100.* When the scale maximum corresponded to a very strong pain instead of an extreme pain, we used a x80 multiplier instead of x100. Expected pain intensities were calculated as the average of the standardized targeted stimulus pain intensities per condition or per cue, and were therefore also standardized. We can illustrate the calculation of expected pain intensity as such: 1) a predictable cue

followed by a targeted stimulus pain intensity of 70 had an expected pain intensity of 70; 2) an unpredictable cue followed by two equiprobable targeted stimulus pain intensities of 30 and 70 had for expected pain intensity 50, the average of 30 and 70. The standardization of expected pain intensity means that *differences in expected pain intensity* is also standardized. Trait and state negative affectivity were standardized because several scales were used in the reviewed studies to quantify negative affectivity. For state negative affectivity, the measures comprised validated and unvalidated questionnaires (see list in the supplementary materials). For trait negative affectivity, the measures comprised only validated questionnaires, either about pain-related fear or anxiety, or about general anxiety (see list in the supplementary materials). For both trait and state negative affectivity, we used the standardization formula: *(score – scale minimum) / (scale maximum – scale minimum)* x *100*. The standardization of trait and state negative affectivity means that *differences in trait negative affectivity* and *differences in state negative affectivity* are also standardized.

Missing Data

Missing data essential for the calculation of effect sizes and standard errors were requested by email to the authors of the studies, and imputed otherwise. If no exact *p*-values were given, but it was only mentioned whether the result was significant or $p \leq \alpha$, then $p = \alpha$ was used during imputation. For papers mentioning only that the effect was not significant ($p > \alpha$), effect sizes were set as null (and excluded from the complete case analyses, see *Analyses* section; 5 effect sizes are concerned and can be consulted in the online dataset available at osf.io/qkwr7). Multiple imputations by chained equation (MICE, [50,113]) with the use of the *mice* R package (using the mice::mice command) were conducted to complete the missing data of the moderators and effect sizes. MICE is a method that fills the missing data of a dataset by using the other columns (the other variables) as predictors. Multiple imputed datasets should be created and then analyzed to create a stable and replicable pooled estimate which we did by using either Rubin's rule ([94,113], mice::pool command) or the harmonic mean *p*-value ([30,125], R package *harmonicmeanp*). Rubin's rule is a method that adjusts the standard error of a pooled estimate for imputation uncertainty. Its computation requires one estimate and associated standard error per imputed dataset. The harmonic mean *p*-value is obtained from combining dependent *p*-values while controlling for the family-wise-error rate. This method was used to pool the *p*-values of the omnibus test of moderator for each imputed dataset. Since we calculated several effect sizes per study, we used multilevel generalized mixed models grouped by independent sample in our MICE approach. Our R code and other MICE parameters can be found on the Open Science Framework (osf.io/qkwr7). To achieve a reasonable level of stability and replicability in all our analyses, we targeted a standard error for our pooled effect size estimates and meta-regression estimates of at least 0.01. Following the 2-stages

method described by von Hippel [118], with a first set of 20 imputed datasets, we estimated the number of imputed datasets needed to reach our desired level of precision (SE < 0.01) to be 51.

Analyses

Funnel plots were made to assess the presence of a publication bias in our original and imputed datasets. All effect sizes (Hedges'g (P-U)) were calculated as the difference in pain intensity or pain unpleasantness ratings in the predictable minus unpredictable condition. We calculated several effect sizes per study whenever it was possible and relevant given the moderators that we wanted to test (see part *Data extraction*). The resulting effect size dependency was handled by conducting three-level random model meta-analyses and meta-regressions [115]. All these analyses were conducted with the R package *metafor* ([119], command: metafor::rma.mv). To verify whether the risk of bias had an impact on the meta-analysis estimates, we realized stratified analyses [82,105], i.e. one analysis with all the effect sizes regardless of their risk of bias, one analysis with only the effect sizes at low risk of bias and one analysis with only the effect sizes at high risk of bias. Both imputed outcomes and moderators were included in the analyses [55]. In addition, we conducted sensitivity analyses with the complete cases to verify whether the results differed with and without the imputations.

After estimating the overall mean effect, we performed a series of single moderator meta-regressions [39,49,112]. When the trait negative affectivity scores differed between the predictable and unpredictable conditions, a situation that occurred for the between-group designs, we used the moderator *difference in trait negative affectivity (P-U)*. On the contrary, when the trait negative affectivity score was identical between the predictable and unpredictable conditions, in within-group designs, the *difference in trait negative affectivity (P-U)* was null (equal zero), so we preferred to use the absolute score that we simply called *trait negative affectivity*. For the other moderators, all effect sizes were used (i.e. those from both within and between design studies). Since previous studies have shown that the pain intensity ratings to (un)predictable stimulations are influenced by targeted stimulus pain intensities and by differences in expected pain intensities between the predictable and unpredictable conditions [13,83,128], we conducted meta-regressions with *targeted stimulus pain intensity* and *difference in expected pain intensity (P-U),* once independently and once in the same model, to try to disambiguate the effects of these two variables from the effect of unpredictability.

We report Hedges' g (P-U) estimates (g) whose significance was tested with a t-distribution (k - p degrees of freedom, k: number of effect sizes, p: numbers of model coefficients, [119]) for the meta-analysis without moderator and for (each level of) the categorical moderators. The significance of the categorical moderators was assessed with omnibus tests of moderator [9,33,119]. For the continuous moderators, we report the pooled regression coefficient ($\hat{\beta}$) whose significance was also assessed with a t-distribution [119]. To evaluate the heterogeneity, we calculated the proportion of observed variance I^2 due to the heterogeneity between and within studies [40,54] as well as the estimated variance σ^2 of

the true effect size between and within studies, and this for each analysis. According to the Cochrane guidelines, we decided to not report the results of the meta-regression analyses when they included less than 9 effect sizes [40].

In addition to the meta-analyses and meta-regressions, we conducted exploratory random forest regressions, a non-parametric type of analysis based on machine learning and using a large set of decision trees to make predictions (using the R-package *metaforest* [116,117]). Each decision tree is built by resampling the original data (with replacement) to form a training set ("in-bag") while the non-used data ("out-of-bag") are kept to form a testing-set. We decided to use this type of analysis because all moderators can be included in the same model, thus enabling random forests analyses to adjust the effects of each moderator to those of the other moderators, including the effects of potential interactions between moderators. This and the non-parametric aspect of the random forest analyses gave them the potential to present a different overview (as compared to the meta-regressions analyses) of the relevant moderators of unpredictable pain perception [116], and this even with small datasets [117]. The outputs of the random forest analyses were not used to assess the significance of effects of the moderators, first because these analyses were exploratory, and second, because the primary goal of our random forest regression analyses is to give an overview of the most important moderators in order to guide the selection of moderators in future research. To be fully transparent, the rankings of the moderators by importance made by the random forests analyses are compared with similar rankings realized with the meta-regression results, thanks notably to explained variances (R^2). We also report the overall performance of the random forest model, for both the training set ("in-bag" explained variance R^2) and the testing set ("out-of-bag" explained variance R^2_{oob}), the former to improve the comparability with the meta-regression results (which are solely training set results), and the latter to show the generalization potential of the model predictions to new data (thus going further than what is done with the meta-regression analyses). Each random forest regression analysis was conducted with 10 000 trees (enough for the mean squared errors MSE to converge), and 4 nodes (randomly picked variables) per tree. One analysis was conducted per imputed dataset and their results were pooled. Since all moderators were tested in the same model in the random forest analyses, *difference in trait negative affectivity (P-U)* and *trait negative affectivity* were tested with all effect sizes (not only with between-group or within-group effect sizes). We added the variable *type of design* in the model (levels: between-group, within-group) to account for possible effects specific to either type of design.

Results

Descriptive statistics and publication bias

Only one study with chronic pain patients fulfilled our inclusion criteria [11]. Three other studies could have been included but provided insufficient data to estimate effect sizes [44,53,70]. Therefore,

we decided to fully focus our systematic review on healthy volunteers (see Table 2 for the list of included studies). We retrieved 67 eligible studies corresponding to 73 independent samples for a total of 2 047 participants. 55% of them were women (1 077/1 965; 68/73 samples provided sex/gender data) and the mean age (mean ± SD) of all participants, men and women, was 23.76 ± 3.65 years (64/73 samples provided age data, 1 880/2 047 participants). Out of the 188 effect sizes retrieved, 137 were considered as being at low risk of bias (pain intensity: 125, pain unpleasantness: 12) and 51 as being at high risk of bias (pain intensity: 46, pain unpleasantness: 5). The funnel plots showed symmetrical effect size distributions, hence suggesting a low risk of publication bias for the analyses without moderator (Figure S1 in the supplementary materials). Before multiple imputation, 68 effect sizes were smaller than -0.1 (minimum: -2.473), 60 were comprised between -0.1 and 0.1, and 50 exceeded 0.1 (maximum: 2.750). After brief inspection of the included studies, we noticed that fear and anxiety showed similar patterns of effects on pain ratings as anticipated (see table S1 in the supplementary materials). Therefore, we decided to continue our analyses as initially planned, that is with fear and anxiety merged under the concept of negative affectivity.

Analyses without moderator

The meta-analyses with the complete cases only and those with the imputed effects sizes showed no overall difference in pain ratings between the predictable and unpredictable conditions, neither for pain intensity ratings nor for pain unpleasantness ratings (Table 3). The amount of heterogeneity within and between studies was reduced in the analyses with the imputed datasets but remained high as shown by the large 95% prediction intervals for the effect of a new study (pain intensity: complete cases: [-0.919;0.865], imputed datasets: [-0.631;0.545]; pain unpleasantness: complete cases: [-2.037;2.563], imputed datasets: [-1.646;1.834]) and for a new effect size within an average study (pain intensity: complete cases: [-0.518;0.464], imputed datasets: [-0.478;0.393]; pain unpleasantness: complete cases: [-0.912;1.438], imputed datasets: [-0.812;1.000]). Stratified analyses with the effect sizes of low and high risk of bias did not reveal any difference in pain ratings between the predictable and unpredictable conditions (Table 3). Forest plots displaying the effect size estimates for each study and the summary estimates of the meta-analyses are available in the supplementary materials, figures S2 and S3.

Meta-regression analyses

To investigate the origin of the high heterogeneity, we conducted a series of meta-regressions with the complete case and with the imputed datasets, reported in Tables 4 and 5. All meta-regressions were conducted regardless of differences in risk of bias as the effect estimates were not found to be statistically significant in the analyses: 1) with all studies; 2) with only the studies with a high risk of bias; 3) with only the studies with a low risk of bias.

Pain intensity ratings, complete case. The complete case analyses revealed that lower targeted stimulus pain intensities were associated with higher pain ratings in unpredictable conditions (negative Hedges'g (P-U)) whereas higher targeted stimulus pain intensities were associated with higher pain ratings in predictable conditions (positive Hedges'g (P-U)) (*targeted stimulus pain intensity*: $\hat{\beta}$ = 0.006 ± 0.002, t(100) = 3.847, p < 0.001; Figure 2A; Table 4). The effect of *difference in expected pain intensity (P-U)* showed that pain intensity ratings were higher in the condition with higher expected pain intensity, regardless of whether this was the predictable or unpredictable condition, (*difference in expected pain intensity (P-U)*:$\hat{\beta}$ = 0.005 ± 0.003, t(94) = 2.131, p = 0.036; Figure 2B). Targeted stimulus pain intensities and expected pain intensities are potential confounders of the effect of unpredictability on pain perception [13,83,128]. Therefore, to try to disambiguate the three effects, we tested targeted stimulus pain intensity and expected pain intensity in the same model, where we selected only Hedges' g's (P-U) corresponding to difference in expected pain intensity (P-U) equal to zero. The results still showed that pain intensity ratings are not significantly higher in the unpredictable conditions relative to the predictable conditions when we control for the other factors, ($\hat{g}$ = -0.100 ± 0.071, t(16) = -1.419, p = 0.175, see the supplementary materials for more details). The conditions, either predictable or unpredictable, which elicited more (state) negative affectivity led to higher pain intensity ratings (*difference in state negative affectivity (P-U)*: $\hat{\beta}$ = 0.020 ± 0.005, t(36) = 3.760, p = 0.001; Figure 2C). Controllability was associated with a trend for higher pain intensity ratings during unpredictable than predictable conditions (negative Hedges' g (P-U)) whereas the absence of controllability was associated with a trend for higher pain intensity ratings during predictable than unpredictable conditions (positive Hedges' g (P-U), see table 4). These two trends were, however, statistically non-significant (*controllability*: g = -0.323 ± 0.180, t(39) = -1.838, p = 0.074; *no controllability*: g = 0.369 ± 0.201, t(39) = -1.794, p = 0.081). The omnibus test of moderator revealed that *controllability*, all levels considered, was not a statistically significant predictor of pain intensity ratings in predictable and unpredictable contexts (F(1,39) = 3.377, p = 0.074).

Pain intensity ratings, imputations. The analyses with the imputed datasets also showed significant effects of *targeted stimulus pain intensity* ($\hat{\beta}$ = 0.005 ± 0.002, t(132.7) = 2.723, p = 0.007) and *difference in expected pain intensity (P-U)* ($\hat{\beta}$ = 0.010 ± 0.003, t(114.6) = 3.775, p < 0.001). As we did for the complete case analyses, we conducted an exploratory meta-regression with the effect sizes from studies where *difference in expected pain intensity (P-U)* did not differ between conditions, in order to disambiguate the effects of expected pain intensity, targeted stimulus pain intensity and unpredictability. The results showed again that unpredictability does not statistically increase pain perception when we control for the other factors, although a tendency in this direction could be noted ($\hat{g}$ = -0.118 ± 0.062, t(59.6) = -1.910, p = 0.061, see the supplementary materials for more details). The studies with ($\hat{g}$ = -0.210 ± 0.137, t(136.9) = -1.538, p = 0.126) and without controllability ($\hat{g}$ = 0.198 ± 0.149, t(136.2) = 1.334, p = 0.186) did not suggest any in-group difference in pain intensity ratings

caused by unpredictability. The harmonic mean *p*-value of the omnibus tests of moderator conducted on each imputed dataset showed that *controllability*, all levels considered, is not a significant predictor of pain intensity ratings in predictable and unpredictable contexts (HMP = 0.107).

Pain unpleasantness ratings. None of the tested moderators significantly moderated the effect of unpredictability on pain unpleasantness ratings, with just the predictor *differences in expected pain intensity (P-U)* approaching significance ($\hat{\beta}$ = 0.002 ± 0.001, t(7) = 2.119, p = 0.072; Table 5).

Moderators ranked by importance

Contrary to the meta-regression analyses, the random forest regression analyses incorporated all the moderators in the same model, in a non-parametric way, and tested whether the effects of these moderators (in the training set, "in-bag" explained variance) could generalize to new studies and effect sizes (testing set, "out-of-bag" explained variance). These features motivated our decision to conduct exploratory random forest analyses in addition to the meta-regressions. We also made use of the random forest analyses to rank the moderators according to their impact on the Hedges' g (P-U) effect sizes. For comparability purposes, we attempted to make similar rankings with the variances explained by the moderators in the meta-regression analyses. Previous research has shown that random forests analyses could be applied to small sample meta-analyses [117]. However, results should be cautiously interpreted because of the lower number of data used in the training and testing sets than typically used for this type of analysis.

Pain intensity ratings. Random forest analyses conducted with the effect sizes for pain intensity ratings disclosed rather disparate performances across datasets ("in bag" R^2 ± SE = 0.186 ± 0.075; "out of bag" R^2 ± SE = 0.065 ± 0.106). According to the random forest analyses, *difference in state negative affectivity (P-U)* ranked as the most important variable, followed by *difference in expected pain intensity (P-U)* and by *trait negative affectivity*. This top three was similar for the meta-regression analyses with the imputed datasets. However, the top three for the meta-regression analyses with the complete cases differed and ranked *difference in trait negative affectivity (P-U)* in first position, *difference in state negative affectivity (P-U)* in second position and *controllability* in third position. We want to precise that *trait negative affectivity* was analyzed in the random forest analyses with all the effect sizes but only with the within-group effect sizes in the meta-regressions analyses, thus possibly explaining its different rankings. Moreover, *trait negative affectivity* was not present in the ranking based on the complete cases meta-regression analyses because of insufficient within-group studies to get reliable results. *Targeted stimulus pain intensity*, previously found as a significant moderator, ranked in 6th position according to the random forest analyses, a position rather congruent with the rankings made with the meta-regressions R^2 (4th position for the complete cases analyses, 5th position for the analyses with the imputed datasets). *Controllability* was found to be the least important moderator according to the random forest analyses. This result differed from the rankings derived from the R^2 of the meta-regressions (3rd position for the

complete cases analyses, 6th position for the analyses with the imputed datasets). This could suggest a poor generalization to new effect sizes, or that the other moderators present in the random forest model better explained its effect. The full rankings can be seen in Table 6 and an illustration of the effect of the most impactful moderators is depicted in Figure 3.

Pain unpleasantness ratings. We conducted the same type of random forest analyses to rank the effects of the moderators on the effect sizes for pain unpleasantness ratings. However, the majority of the models showed negative "out-of-bag" explained variances ($R^2 \pm SE = -0.183 \pm 0.193$) and positive "in-bag" explained variances ($R^2 \pm SE = 0.525 \pm 0.181$) suggesting overfitting in the trained model. This might have been caused by an insufficient number of effect sizes (17 effect sizes from 12 independent samples) to properly train the models and to cross validate their performances. For this reason, we decided to not report the rankings of the moderators for the effect sizes referring to pain unpleasantness ratings.

Discussion

In this systematic review and meta-analysis, we have investigated the effect of unpredictability on pain perception and its modulation by potentially relevant moderators. We did not find any statically significant effects of unpredictability on ratings of pain intensity and pain unpleasantness. Moreover, the meta-regression analyses showed significant moderating effects of targeted stimulus pain intensity, (difference in) expected pain intensity, and (difference in) state negative affectivity on the effects of unpredictability on pain intensity ratings. The random forest regressions mitigated the findings for targeted stimulus pain intensity and added trait negative affectivity as one of the most important moderating variables. The other moderators: (difference in) anticipation delay, stimulus duration, sex/gender, age, method of pain induction and type of unpredictability showed all non-significant effects. For pain unpleasantness ratings, we did not identify any significant moderator, presumably due to the smaller number of studies reporting this outcome.

Unpredictable is not more painful

Despite the common assumption, we could not find that, in healthy human volunteers, unpredictability alone significantly increases pain perception. We also observed that safety signaling [100,101], that is the predictability of pain onset involving the predictability of phases without pain, did not appear to reduce pain perception, as shown by the absence of significant difference between the conditions with predictable and unpredictable pain onsets. Since previous work showed that the effect of unpredictability could be (at least partially) explained by expectations and targeted stimulus pain intensity [13,83,128], we tried to control for these variables in our analyses. However, we did not find any significant direct effect of unpredictability on pain intensity ratings even when controlling for these

variables. Furthermore, our results showed that higher pain ratings in the unpredictable relative to the predictable conditions are essentially favored by higher expected pain intensities and higher state negative affectivity in the unpredictable conditions, as well as by high targeted stimulus pain intensity. To a lesser extent, which remains to be confirmed, higher pain ratings in the unpredictable conditions might also be favored by controllability and by high trait negative affectivity.

Targeted stimulus pain intensity and expectations

Targeted stimulus pain intensity was measured to verify whether effects of unpredictability could vary with pain intensity levels (such as low, medium or high pain intensity, see [13,83] for examples). To avoid making arbitrary categories, we decided to keep this variable continuous. We calculated its values by using the pain ratings during calibration, or when unavailable, by averaging the ratings across all experimental studies (see supplementary materials for examples). Only pain ratings to identical stimulus intensities were averaged such that all averaged pain ratings and the resulting average estimate approximately represented the same level of pain intensity. Moreover, the estimates were calculated with ratings per condition at the study level, and not at the individual level, hence a reduced risk of large discrepancies between conditions. Overall, we estimated the imprecision due to our method of estimation as being at a known low level of risk of bias, and preferable to multiple imputations with unknown (probably low) risk of bias. Indeed, simulations proved that pooling the results from multiple imputed datasets has a low risk of bias (Van Buuren et al., 2011, Von Hippel, 2018), but the risk of bias cannot be formally assessed outside simulations because of the complexity and opacity of multiple imputation algorithms. Therefore, we decided to impute targeted stimulus pain intensity only when no other estimation could be made.

Regarding the results, we observed significant moderating effects of targeted stimulus pain intensity and expectations as previously found in the literature [13,41,45,51,83,128,132], and that for both analyses with and without imputations. The random forest rankings of the moderators suggest that the effect of expected pain intensity is more important than the effect of targeted stimulus pain intensity, whereas more ambiguous rankings were found with the meta-regression analyses. Notably, as compared to targeted stimulus pain intensity, the fact that (differences in) expected pain intensity appear as a more important variable in the random forest rankings, could suggest that its effects are more generalizable to new effect sizes and studies, and less susceptible to be explained by the other moderators. Our findings are congruent with previous literature proposing that expectations are intrinsically affected by many unpredictability manipulations and that they may explain why unpredictability sometimes enhances pain perception [128]. Thus, in studies investigating unpredictability, we recommend to be particularly careful to not misinterpret differences in pain ratings actually due to differences in expected pain intensities for a direct effect of unpredictability.

Negative affectivity

Fear and anxiety are thought to be differently associated with (un)predictability, with fear being more closely related to predictability, and anxiety to unpredictability [31,60,92], even if consensus is lacking [60,74]. Fear and anxiety were also theorized and sometimes found to have opposite effects on pain perception [31,92]. However, other empirical studies showed contrasted findings with either no clear associations between pain and fear and pain and anxiety [6,7,69] or with positive correlations with pain perception for both emotions [27,71].

In the present meta-analysis, we decided to merge fear and anxiety under the construct of negative affectivity. The rationale behind this decision was primarily based on the doubts we had about participants' ability to accurately distinguish and report the two emotions. Since the appraisals of fear and anxiety are characterized by subtle differences in the degree of certainty and imminence of a threat [103] a possible co-activation and confusion of both emotions can occur in participants. Several similarities between the physiological responses to fear and anxiety [56] also question the extent to which they can be discriminated at the interoceptive level by the participants. A stronger sense of fear, associated with freezing responses, might induce a physiological pattern easily recognizable and distinct from behavioral anxiety responses [56], but these situations are hard to elicit with experimental painful stimulations in healthy human volunteers, notably because of safety constraints in experiments. Lastly, we noticed that not all studies report whether a systematic explanation of the difference between fear and anxiety was given to participants to help the distinction.

In the present work, the decision to merge fear and anxiety was supported by the synthesis of their effects on unpredictable pain perception (Table S1, supplementary materials) and by our finding that the conditions, either predictable or unpredictable, with higher state negative affectivity are associated with higher pain intensity ratings. These results might suggest that either fear and anxiety have different effects on (un)predictable pain perception, at least for healthy volunteers in laboratory settings, or that the widely used self-reports of fear and anxiety often fail to distinguish the two emotions (for the reasons aforementioned). In the latter case, providing participants with systematic explanations of the difference between fear and anxiety in order to help them distinguish the two emotions could possibly improve self-reports, and that not only in studies measuring the two emotions but also in studies measuring only one of them.

Limitations

The first limitation lies in the necessity to standardize some variables across studies. As a consequence, the moderators tested in our analyses may have lost validity compared to the original

scores. This standardization process was however necessary to compare the results of studies using various pain induction methods and measurement systems. This limitation might be overcome in future systematic reviews or meta-analyses focusing on subsets of similar studies.

We operationalized expectations as the average of the received targeted stimulus pain intensities per condition or cue. This choice was motivated by the ease of access to these data and because this conceptualization of expectation was previously found to be a relevant predictor of pain [24,45,90]. However, a growing body of research has shown that expectations dynamically fluctuate over time [72,77,83]. Yet our current operationalization of expectations considers them as fixed, not as dynamic. Therefore, the effects of expectations could be more important than found in this meta-analysis.

Previous systematic reviews found positive associations between trait negative affectivity and pain perception [64,68,108]. However, our results do not show any clear effect on the pain ratings in (un)predictable context. The small number of studies focusing at the same time on unpredictability, pain and negative affectivity may have contributed to the unclarity of the results. Besides, the effects of trait negative affectivity may appear only beyond a certain (high) threshold [69] and be therefore hard to capture in experimental studies in non-clinical samples.

Controllability probably suffered as well from the small number of included studies giving actual control or an illusion of control over pain to the participants in a context of unpredictable pain manipulation. Its results shortly failed to reach significance but showed tendencies in the expected direction, namely lower pain intensity ratings in the predictable condition when participants were given control and higher pain intensity ratings in the unpredictable condition when they were not given control. Since controllability reduces state negative affectivity [67], its effect could be partially explained by state negative affectivity, especially in the random forest analyses.

We aimed at investigating the effects of unpredictability on pain perception in healthy volunteers and patients. However, our analyses only concerned healthy volunteers because of the insufficient number of studies with clinical samples, which stresses the need for future research in this area.

Finally, previous evidence has revealed that patients (e.g. with fibromyalgia) could perceive unpredictable pain as more intense than predictable pain [11]. This might be related to differences between real-life and experimental settings, the latter being less threatening than the real-life situations experienced by patients. Moreover, pain in real-life contexts may also enter into conflict with goal pursuit, a major aspect to consider in the cognitive and affective responses to pain [98,114], which deserves future study.

Conclusion

The present meta-analysis suggests no direct effect of unpredictability on the perception of pain in healthy individuals. In contrast, targeted stimulus pain intensity, expected pain intensity and state negative affectivity may constitute moderating variables. This means that non-controlled differences between the predictable and unpredictable pain conditions on one or more of these variables are capable of confounding interferences regarding the effect of unpredictability on pain intensity ratings. Controllability and trait negative affectivity show interesting but unclear results, thus requiring more investigations. Regarding pain unpleasantness ratings, we did not identify any significant moderator, probably because of insufficient data. Overall, this systematic review and meta-analysis focused on a very broad definition of unpredictability and is a first attempt to clarify our understanding of the effects of (un)predictability on pain perception in laboratory studies. We also focused only on healthy volunteers because of an insufficient number of experimental studies focusing on the perception of unpredictable pain in clinical samples, which calls for more research in this area.

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Tables

Taxonomy by Imada and Nageishi [46]	Taxonomy by Miller [70]	Taxonomy in the present manuscript
Signaled vs. unsignaled aversive stimuli	Onset	**Onset**
Fixed vs. variable temporal intervals	Onset	**Onset**
Fixed vs. variable stimulus number	-	**Duration**
Fixed vs. variable stimulus duration	Event	**Duration**
Fixed vs. variable stimulus intensity	Event	**Intensity**
Fixed vs. variable cue-stimulus interval	Onset	**Onset**
Fixed vs. variable cue intensity	-	-
Fixed vs. variable stimulus quality, pattern and locus	Event	**Quality*** **Pattern*** **Location**
Fixed vs. variable cue quality, pattern and locus	-	-

Table 1. Taxonomy of unpredictable stimulus features (modified from Zaman et al. [124] with authorization). * no article found with these types of unpredictability

sample ID	Reference	n effect sizes		type of unpred.	meth. pain induct.	n women	n men	mean age	ROB
		pain int.	pain unpl.						
Arendsen 2018 [1]	Arendsen et al., 2018		2	intensity	pressure	20	3	21.4	low
Arntz 1988 [2]	Arntz & van den Hout, 1988	1		intensity	electrical	7	12	21.7	low
Arntz 1990 [3]	Arntz et al., 1990	1		intensity	electrical	22	4	20.0	high
Atlas 2022 [4]	Atlas et al. 2022	3		intensity	thermal	22	18	27.0	low
Bąbel 2018 [5]	Bąbel et al., 2018	1		intensity	electrical	60	0	23.5	low
Bajcar 2020 pain med [7]	Bajcar et al., 2020 a	2		intensity	electrical	39	0	23.8	low
Bajcar 2020 plos one high fear [6]	Bajcar et al., 2020 b	2		intensity	electrical	31	0	23.8	low
Bajcar 2020 plos one low fear [6]	Bajcar et al., 2020 b	2		intensity	electrical	28	0	23.8	low
Bélanger 2017 [8]	Bélanger et al., 2017	8		onset	electrical	10	10	22.5	low
Bowers 1971 [10]	Bowers, 1971	1		onset	electrical	0	8		low
Bradshaw 2012 [11]	Bradshaw et al., 2012	4		intensity	pressure	10	0	24.4	low
Bräscher 2016 [12]	Bräscher et al., 2016	1		intensity	thermal	10	13	24.2	high
Brown 2008 [13]	Brown et al., 2008	2		intensity	thermal			47.0	high
Carlino 2015 [14]	Carlino et al., 2015	2		intensity	thermal	14	20	23.0	low
Carlsson 2006 main [15]	Carlsson et al., 2006	2	2	onset	electrical	5	4	25.0	high
Carlsson 2006 pilot [15]	Carlsson et al., 2006	2	2	onset	electrical	3	7	24.0	low
Clark 2008 [16]	Clark et al., 2008	1		onset	thermal			21.2	high

Colagiuri 2015 [17]	Colagiuri et al., 2015	2		intensity	electrical	22	18	20.3	high
Elliott 1975 [23]	Elliot, 1975	1		onset	electrical	0	32		high
Forkmann 2016 [26]	Forkmann et al., 2016	1		onset	thermal	12	12	28.4	low
Gondo 2012 [29]	Gondo et al., 2012		1	intensity	electrical	12	6	29.3	low
Harvie 2016 [32]	Harvie et al., 2016	1		intensity	electrical	31	23	26.0	high
Helmchen 2006 [34]	Helmchen et al., 2006	2		onset	thermal	0	16	26.4	1 high 1 low
Henderson 2020 [35]	Henderson et al., 2020	3		intensity	thermal	11	9	22.0	high
Hird 2019 [42]	Hird et al., 2019	3		intensity	electrical	19	12	23.0	low
Holten-Rossing 2018 [43]	Holten-Rossing et al., 2018	1	1	intensity	thermal	4	7	34.3	low
Hoskin 2019 exp 1 [45]	Hoskin et al., 2019	13		intensity	electrical	14	2	19.6	low
Hoskin 2019 exp 2 [45]	Hoskin et al., 2019	4		intensity	electrical	26	6	19.3	low
Iannetti 2008 [46]	Iannetti et al., 2008	4		intensity	thermal	2	5	29.0	low
Icenhour 2017 [47]	Icenhour et al., 2017	1		onset	mech. distention	20	16	25.1	low
Kissi 2021 [52]	Kissi et al., 2021	1		onset	electrical	40	14	22.0	high
Labrenz 2016 [57]	Labrenz et al., 2016	1		onset	mech. distention	25	24	25.3	low
Lev 2012 [61]	Lev et al., 2012	2		onset	thermal	18	4	33.0	low
Lim 2020 [62]	Liv et al., 2020	4		intensity	thermal	21	21	31.2	3 high 1 low
Lin 2014 [63]	Lin et al., 2014	2		intensity	electrical	8	6	27.3	low
Löffler 2018 sample 1 [65]	Löffler et al., 2018	1	1	duration	electrical	13	13	25.5	high
Löffler 2018 sample 2 [65]	Löffler et al., 2018	1	1	duration	electrical	17	8	25.3	high
Loued-Khenissi 2022 [66]	Loued-Khenissi et al., 2022	2		onset	thermal	26	17	23.7	high
Metzger 2019 [69]	Metzger et al., 2019	2		onset	electrical				low
Meulders 2012 [71]	Meulders et al., 2012	1	1	onset	electrical	31	20	20.0	low
Mohr 2005 [75]	Mohr et al., 2005	1		onset	thermal	0	16	26.4	low
Mohr 2008 [76]	Mohr et al., 2008	2		onset-duration	thermal	0	17	26.3	high
Müller 2012 [78]	Müller, 2012	1	1	onset	electrical	0	64	25.1	high
Müller 2013 [79]	Müller, 2013	1		onset	electrical	0	50	24.6	high
Neige 2020 [80]	Neige et al., 2020	2		onset	thermal	10	10	26.0	low
Oka 2010 [81]	Oka et al., 2010	8		4 onset 4 intensity	electrical	25	0		high
Peng 2019 j neurosci [85]	Peng et al., 2019 a	2		intensity	electrical	15	15	20.5	low
Peng 2019 soc cogn affect neurosci [84]	Peng et al., 2019 b	2	2	intensity	electrical	23	20	20.5	low
Pervin 1963 [86]	Pervin, 1963	2		onset	electrical	0	30		high
Piedimonte 2017 [88]	Piedimonte et al., 2017	1		intensity	electrical	18	16	23.0	low
Ploghaus 2001 [89]	Ploghaus et al., 2001	1		intensity	thermal	0	8		low
Quelhas Martins 2015 [91]	Quelhas-Martins et al., 2015	5		intensity	electrical	43	33	19.7	low
Rubio 2015 [95]	Rubio et al., 2015		1	onset	mech. distention	9	6	24.0	low
Salomons 2007 [96]	Salomons et al., 2007	1		intensity-duration	thermal	5	11	22.0	high
Salomons 2015 [97]	Salomons et al., 2015	1		intensity-duration	thermal	26	26	20.5	high
Shih 2019 [102]	Shih et al., 2019	7		intensity	electrical	10	13	24.1	low
Staub 1971 exp1 [104]	Staub et al., 1971	1		onset	electrical				high
Staub 1971 exp2 [104]	Staub et al., 1971	1		onset	electrical				high
Swider 2019 [106]	Swider et al., 2019	2		onset	electrical	28	0	23.7	low
Tang 2005 [107]	Tang & Gibson, 2005	1		intensity	electrical	19	13	24.3	low
Torta 2012 [109]	Torta et al., 2012	1		location	thermal	5	6	29.8	high

Tracy 2017 [110]	Tracy et al., 2017	2	2	intensity	thermal	26	26	21.9	low
Wang 2010 [120]	Wang et al., 2015	4		onset	thermal	7	3	29.0	low
Weisenberg 1985 [122]	Weisenberg et al., 1985	1		onset	electrical	0	42	24.3	high
Wiech 2006 [123]	Wiech et al., 2006	1		duration	electrical	12	0	24.0	high
Wiech 2014 [124]	Wiech et al., 2014	2		duration	electrical	7	5	29.9	high
Yeung 2014 [125]	Yeung et al., 2014	2		intensity	electrical	12	8	19.8	low
Yoshida 2013 [127]	Yoshida et al., 2013	1		intensity	thermal	9	8		low
Zaman 2017 [129]	Zaman et al., 2017	1		intensity	electrical	29	9	22.6	low
Zaman 2019 [132]	Zaman et al., 2019	1		intensity	electrical	28	9	21.8	low
Zaman 2022 Instruct [130]	Zaman et al., 2022	12		intensity	electrical	28	12	20.6	low
Zaman 2022 Learn [130]	Zaman et al., 2022	12		intensity	electrical	23	17	20.2	low
Ziv 2010 [134]	Ziv et al., 2010	1		onset	thermal	7	5	24.5	low

Table 2. List of included studies. sample ID: list of independent samples identified with the name of the first author, the year of publication and, when needed, an extra information for disambiguation. n effect sizes: number of effect sizes extracted. pain int.: pain intensity effect sizes. pain unpl.: pain unpleasantness effect sizes. type of unpred.: type of unpredictability manipulated in the study. n women: number of women in the sample. n men: number of men in the sample. ROB: risk of bias. See the full dataset at osf.io/c4gph for more details.

COMPLETE CASES											
PAIN INTENSITY	**n eff.size**	**n samp.**	**g**	**SE**	**t**	**df**	**p**	**I^2 btw**	**I^2 with**	**σ^2 btw**	**σ^2 with**
All ROB	104	41	-0.027	0.081	-0.334	40	0.741	84.5	13.9	0.207	0.034
High ROB	13	11	-0.096	0.335	-0.288	10	0.779	97.0	15.8	1.147	0.003
Low ROB	91	30	0.006	0.073	0.078	29	0.938	74.3	23.2	0.109	0.034
UNPLEASANT.	**n eff.size**	**n samp.**	**g**	**SE**	**t**	**df**	**p**	**I^2 btw**	**I^2 with**	**σ^2 btw**	**σ^2 with**
All ROB	9	7	0.263	0.447	0.588	6	0.578	99.4	0.3	1.377	0.004
High ROB	3	3	-0.200	0.375	-0.533	2	0.647	48.3	48.3	0.197	0.197
Low ROB	6	4	0.624	0.720	0.867	3	0.450	99.6	0.2	2.056	0.004
WITH IMPUTATIONS											
PAIN INTENSITY	**n eff.size**	**n samp.**	**g**	**SE**	**t**	**df**	**p**	**I^2 btw**	**I^2 with**	**σ^2 btw**	**σ^2 with**
All ROB	171	70	-0.043	0.052	-0.817	155.7	0.415	46.1	51.6	0.090	0.1
High ROB	46	28	-0.146	0.112	-1.305	37.9	0.2	22.9	74.3	0.082	0.267
Low ROB	125	44	0.017	0.058	0.296	119	0.768	54.2	43.2	0.082	0.066
UNPLEASANT.	**n eff.size**	**n samp.**	**g**	**SE**	**t**	**df**	**p**	**I^2 btw**	**I^2 with**	**σ^2 btw**	**σ^2 with**
All ROB	17	12	0.094	0.265	0.353	14.3	0.729	95.6	4.0	0.788	0.033
High ROB	5	4	-0.266	0.234	-1.136	2.8	0.342	10.1	85.1	0.028	0.21
Low ROB	12	8	0.276	0.369	0.748	9.4	0.472	98.7	0.90	1.048	0.01

Table 3. Meta analyses results stratified by the risk of bias. ROB: risk of bias; n eff.size: number of effect sizes included; n samp: number of independent samples; $\hat{g}$: overall effect size estimate; SE: standard error; t: value of the univariate Wald test ; df: degrees of freedom; I^2 btw: proportion of heterogeneity between studies (range: 0-100) averaged across the 51 imputed datasets; I^2 with: proportion of heterogeneity within studies (range: 0-100) averaged across the 51 imputed datasets; σ^2 btw: estimated variance of the true effect size between studies averaged across the 51 imputed datasets; σ^2 with: estimated variance of the true effect size within studies averaged across the 51 imputed datasets.

COMPLETE CASES

moderator	omnibus test	levels	n eff.size	n samp.	g	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
control.	F(1,39) = 3.377 p = 0.074	control	10	9	-0.323	0.180	t(39) = -1.794	0.081	84.0	14.3	0.200	0.034
		no control	94	31	0.369	0.201	t(39) = 1.838	0.074				
meth. pain induct.	F(2,38) = 0.335 p = 0.717	electrical	84	27	-0.072	0.102	t(38) = -0.702	0.487	85.1	13.3	0.218	0.034
		thermal	18	12	0.113	0.183	t(38) = 0.617	0.540				
		pressure	0	0			NA					
		mech. dist.	2	2	0.265	0.430	t(38) = 0.616	0.540				
type of unpred	F(2,38) = 0.024 p = 0.976	intensity	79	26	-0.003	0.139	t(103) = -0.020	0.984	85.2	13.1	0.221	0.034
		onset	22	12	-0.043	0.219	t(38) = -0.195	0.847				
		duration	5	5	-0.012	0.156	t(38) = -0.075	0.940				
		location	0	0			NA					

moderator	n eff.size	n samp.	β	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
diff. anticip. Delay (P-U)	74	29	0.002	0.015	t(72) = 0.143	0.887	73.8	23.9	0.121	0.039
diff. expect. pain int. (P-U)	96	34	0.005	0.003	t(94) = 2.131	**0.036**	75.1	22.1	0.112	0.033
diff. state neg. aff. (P-U)	38	12	0.021	0.005	t(36) = 4.431	**0.001**	82.6	15.1	0.108	0.02
diff. trait neg. aff. (P-U)	10	7	-0.072	0.070	t(14) = -1.023	0.324	83.5	5.1	0.261	0.016
trait neg. aff.	4	3			<9 effect sizes					
duration	99	36	-0.016	0.014	t(34) = -1.193	0.241	81	16.9	0.162	0.034
sex/gender	100	39	0.102	0.307	t(37) = 0.333	0.741	83.7	14.5	0.197	0.034
age	99	37	-0.009	0.019	t(97) = -0.510	0.611	84.7	13.6	0.212	0.034
targeted stim. pain int.	102	39	0.006	0.002	t(100) = 3.847	**<0.001**	81.2	16.1	0.126	0.025

WITH IMPUTATIONS

moderator	omnibus test	levels	n eff.size	n samp.	$\hat{g}$	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
control.	HMP = 0.107	control	17	14	-0.210	0.137	t(136.9) = -1.538	0.126	46.2	51.4	0.09	0.100
		no control	154	57	0.198	0.149	t(136.2) = 1.334	0.184				
meth. pain induct.	HMP = 0.562	electrical	120	43	-0.095	0.067	t(147.9) = -1.403	0.163	46.6	51.1	0.092	0.100
		thermal	45	24	0.137	0.111	t(158.2) = 1.229	0.221				
		pressure	4	1	0.026	0.381	t(164.5) = 0.067	0.947				
		mech. dist.	2	2	0.286	0.386	t(164.6) = 0.740	0.460				
type of unpred	HMP = 0.972	intensity	114	38	-0.001	0.113	t(164.4) = -0.010	0.992	46.9	50.7	0.094	0.101
		onset	51	28	-0.015	0.122	t(161.9) = -0.120	0.904				
		duration	9	7	-0.037	0.111	t(166.7) = -0.328	0.743				
		location	1	1	0.037	0.524	t(168.9) = 0.070	0.945				

moderator	n eff.size	n samp.	β	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
diff. anticip. delay (P-U)	171	70	-0.001	0.021	t(61.4) = -0.033	0.974	45.8	51.9	0.089	0.101
diff. expect. pain int. (P-U)	171	70	0.010	0.003	t(114.6) = 3.375	0.000	49.3	48.2	0.088	0.086
diff. state neg. aff. (P-U)	171	70	0.008	0.005	t(15.6) = 1.625	0.124	49.7	47.7	0.089	0.084
diff. trait neg. aff. (P-U)	32	20	-0.059	0.087	t(23.0) = -0.677	0.505	85.1	1.9	0.438	0.01
trait neg. aff.	139	52	-0.010	0.006	t(26.5) = -1.504	0.145	27.7	69.4	0.038	0.092
duration	171	70	-0.008	0.010	t(149.3) = -0.841	0.402	46.6	51.1	0.091	0.100
sex/gender	171	70	-0.107	0.199	t(127.9) = -0.537	0.592	45.6	52.0	0.089	0.101
age	171	70	-0.005	0.012	t(119.4) = -0.437	0.663	46.7	51.0	0.092	0.100

targeted stim. pain int.	171	70	0.005	0.002	t(132.7) = 2.723	0.007	50.7	46.9	0.097	0.090

Table 4. Results of meta regression analyses for pain intensity effect sizes. Omnibus test: omnibus test of moderator reported here with the F statistic and the *p*-value for complete cases, and a harmonic mean p-value HMP for the analyses with the 51 imputed datasets; n eff.size: number of effect sizes included; n samp: number of independent samples; $\hat{g}$: pooled effect size estimate. Negative numbers indicate higher pain ratings in the unpredictable condition and positive numbers indicate higher pain ratings in the predictable condition; $\hat{\beta}$: regression coefficients; SE: standard error; test statistic: value of the univariate Wald test; I^2 btw: proportion of heterogeneity between studies (range: 0-100); I^2 with: proportion of heterogeneity within studies (range: 0-100); σ^2 btw: estimated variance of the true effect size between studies averaged across the 51 imputed datasets; σ^2 with: estimated variance of the true effect size within studies averaged across the 51 imputed datasets: control: controllability; type of unpred: type of unpredictability; mech dist: mechanical distention; diff. anticip. delay (P-U): difference in average anticipation delay between the predictable and unpredictable condition; diff. expect. pain int (P-U).: difference in expected pain intensity between the predictable and unpredictable condition; diff. state neg. aff. (P-U): difference in state negative affectivity (fear and anxiety) between the predictable and unpredictable condition; diff. trait neg. aff. (P-U): difference in trait negative affectivity score between the predictable and unpredictable condition (only for between-group studies); trait neg. aff.: trait negative affectivity score (only for within-group studies; targeted stim. pain int.: targeted stimulus pain intensity

COMPLETE CASES

moderator	omnibus test	levels	n eff.size	n samp	g	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
control.	F(1,5) = 0.861 p = 0.396	control	3	3	-0.225	0.694	t(5) = -0.325	0.759	99.4	0.3	1.414	0.004
		no control	6	4	0.850	0.916	t(5) = 0.928	0.396				
meth. pain induct.	F(1,5) = 0.012 p = 0.919	electrical	7	6	0.283	0.528	t(5) = 0.536	0.615	99.5	0.2	1.649	0.004
		thermal	2	1	-0.150	1.403	t(5) = -0.107	0.919				
		pressure	0	0			NA					
		mech. dist.	0	0			NA					
type of unpred	F(2,4) = 0.336 p = 0.733	intensity	5	3	-0.003	0.139	t(103) = -0.020	0.984	85.2	13.1	0.221	0.034
		onset	2	2	-0.043	0.219	t(38) = -0.195	0.847				
		duration	2	2	-0.012	0.156	t(38) = -0.075	0.940				
		location	0	0			NA					

moderator	n eff.size	n samp	β	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
diff. anticip. delay (P-U)	7	5			Only null delays					
diff. expect. int. (P-U)	9	7	0.002	0.001	t(7) = 2.119	0.070	99.5	0.0	1.38	0.0
diff. state neg. aff. (P-U)	3	2			<9 effect sizes					
diff. trait neg. aff. (P-U)	1	1			<9 effect sizes					
trait neg. aff.	1	1			<9 effect sizes					
duration	6	4			<9 effect sizes					
sex/gender	9	7	2.434	2.044	t(5) = 1.191	0.290	99.4	0.3	1.289	0.062
age	9	7	-0.210	0.128	t(5) = -1.628	0.170	99.2	0.4	1.077	0.004
targeted stim. pain int.	9	7	0.028	0.015	t(7) = 1.812	0.110	0.0	99.1	0.0	0.819

WITH IMPUTATIONS

moderator	omnibus test	levels	n eff.size	n samp	$\hat{g}$	SE	test statistic	p	I^2 btw	I^2 with	σ^2 btw	σ^2 with
control.	HMP = 0.525	control	3	3	-0.219	0.547	t(13.3) = 0.695	0.695	95.8	3.7	0.836	0.032
		no control	14	9	0.416	0.631	t(13.3) = 0.521	0.521				
meth. pain induct.	HMP = 0.989	electrical	11	8	0.132	0.373	t(11.4) = 0.729	0.729	96.8	2.9	1.07	0.032
		thermal	3	2	-0.043	0.842	t(11.4) = 0.960	0.960				

		pressure	2	1	-0.384	1.119	t(11.4) = 0.738	0.738				
		mech. dist.	1	1	-0.010	1.178	t(11.4) = 0.993	0.993				
type of unpred	HMP = 0.854	intensity	8	5	-0.250	0.827	t(12.4) = 0.768	0.768	96.2	3.3	0.935	0.032
		onset	8	5	0.102	0.830	t(12.3) = 0.904	0.904				
		duration	2	2	0.156	0.698	t(12.4) = 0.827	0.827				
		location	0	0	NA							

moderator	**n eff.size**	**n samp**	**β**	**SE**	**test statistic**	**P**	**I^2 btw**	**I^2 with**	**σ^2 btw**	**σ^2 with**
diff. anticip. delay (P-U)	17	12	-0.117	1.016	t(1.1) = -0.115	0.926	74.1	23.6	0.381	0.035
diff. expect. int. (P-U)	17	12	0.003	0.004	t(13.2) = 0.619	0.546	94.2	5.2	0.778	0.043
diff. state neg. aff. (P-U)	17	12	0.022	0.012	t(5.2) = 1.782	0.133	98.0	1.5	0.796	0.012
diff. trait neg. aff. (P-U)	3	2	too much missing information for reliable imputation							
trait neg. aff.	14	10	too much missing information for reliable imputation							
duration	17	12	-0.013	0.056	t(12.5) = -0.231	0.821	95.8	3.7	0.848	0.033
sex/gender	17	12	1.369	1.294	t(13.3) = 1.059	0.309	95.5	4.0	0.782	0.032
age	17	12	-0.082	0.068	t(13.3) = -1.205	0.249	95.3	4.1	0.752	0.032
targeted stim. pain int.	17	12	0.000	0.004	t(12.1) = -0.057	0.955	94.5	4.9	0.787	0.041

Table 5. Results of meta regression analyses for unpleasantness effect sizes. Omnibus test: omnibus test of moderator reported here with the F statistic and the *p*-value for complete cases, and a harmonic mean p-value HMP for the analyses with the 51 imputed datasets; n eff.size: number of effect sizes included; n samp: number of independent samples; $\hat{g}$: pooled effect size estimate. Negative numbers indicate higher pain ratings in the unpredictable condition and positive numbers indicate higher pain ratings in the predictable condition; $\hat{\beta}$: regression coefficients; SE: standard error; test statistic: value of the univariate Wald test; I^2 btw: proportion of heterogeneity between studies (range: 0-100); I^2 with: proportion of heterogeneity within studies (range: 0-100); σ^2 btw: estimated variance of the true effect size between studies averaged across the 51 imputed datasets; σ^2 with: estimated variance of the true effect size within studies averaged across the 51 imputed datasets: control: controllability; meth. pain induct.: method of pain induction; type of unpred: type of unpredictability; mech dist: mechanical distention; diff. anticip. delay (P-U): difference in average anticipation delay between the predictable and unpredictable condition; diff. expect. pain int (P-U).: difference in expected intensity between the predictable and unpredictable condition; diff. state neg. aff. (P-U): difference in state negative affectivity (fear and anxiety) between the predictable and unpredictable condition; diff. trait neg. aff. (P-U): difference in trait negative affectivity score between the predictable and unpredictable condition (only for between-group studies); trait neg. aff.: trait negative affectivity score (only for within-group studies; targeted stim. pain int.: targeted stimulus pain intensity.

Meta-regression analyses				**Random forest analyses**	
Complete cases		**Imputed datasets**		**Imputed datasets**	
Moderators	**R^2**	**Moderators**	**R^2**	**Moderators**	**importance**
diff. trait neg. aff. (P-U)	0.372	diff. state neg. aff. (P-U)	0.087	diff. state neg. aff. (P-U)	0.035
diff. state neg. aff. (P-U)	0.288	diff. expect. pain int. (P-U)	0.072	diff. expect. pain int (P-U)	0.019
controllability	0.055	trait neg. aff.	0.068	trait neg. aff.	0.018
targeted stim. pain int..	0.053	diff. trait neg. aff. (P-U)	0.047	age	0.010
diff. expect. pain int. (P-U)	0.027	targeted stim. pain int.	0.023	sex/gender	0.009
duration	0.017	controllability	0.017	targeted stim. pain int.	0.007
age	0.011	meth. pain induct.	0.011	duration	0.006
type of unpred.	0.004	sex/gender	0.008	meth. pain induct.	0.003
diff. anticip. delay (P-U)	0.000	age	0.006	diff. anticip. delay (P-U)	0.003
meth. pain induct.	-0.001	diff. anticip. delay (P-U)	0.005	type of unpred.	0.002
sex/gender	-0.001	duration	0.002	diff. trait neg. aff. (P-U)	0.002

-	-	type of unpred.	0.002	type of design	0.002
-	-	-	-	controllability	0.000

Table 6. Moderator rankings for pain intensity effect sizes. For the meta-regression analyses, the explained variances of the moderators (R^2) were used to make the rankings. For the random forest analyses, the build-in permutation method was used to estimate the importance of the moderators and to make the rankings. Contrary to the rankings made with meta-regressions, the random forest rankings took into consideration possible interactions between moderators. meth. pain induct.: method of pain induction; type of unpred: type of unpredictability; diff. anticip. delay (P-U): difference in average anticipation delay between the predictable and unpredictable condition; diff. expect. pain int. (P-U): difference in expected intensity between the predictable and unpredictable condition; diff. state neg. aff. (P-U): difference in state negative affectivity (fear and anxiety) between the predictable and unpredictable condition; diff. trait neg. aff. (P-U): difference in trait negative affectivity (fear and anxiety) between the predictable and unpredictable condition. For the meta-regression analyses, only the between design studies and effect sizes were analyzed. targeted stim. pain int..: targeted stimulus pain intensity. trait neg. aff.: trait negative affectivity score. For the meta-regression analyses, only within design studies and effect sizes were analyzed. type of design.: within-group or between-group. In the random forest analyses, "trait negative affectivity" and "differences in trait negative affectivity" could not be respectively restricted to within and between designs effect sizes only. This variable was added to better take into consideration the effects of "trait negative affectivity" and "differences in trait negative affectivity" while also considering the type of design.

Figures

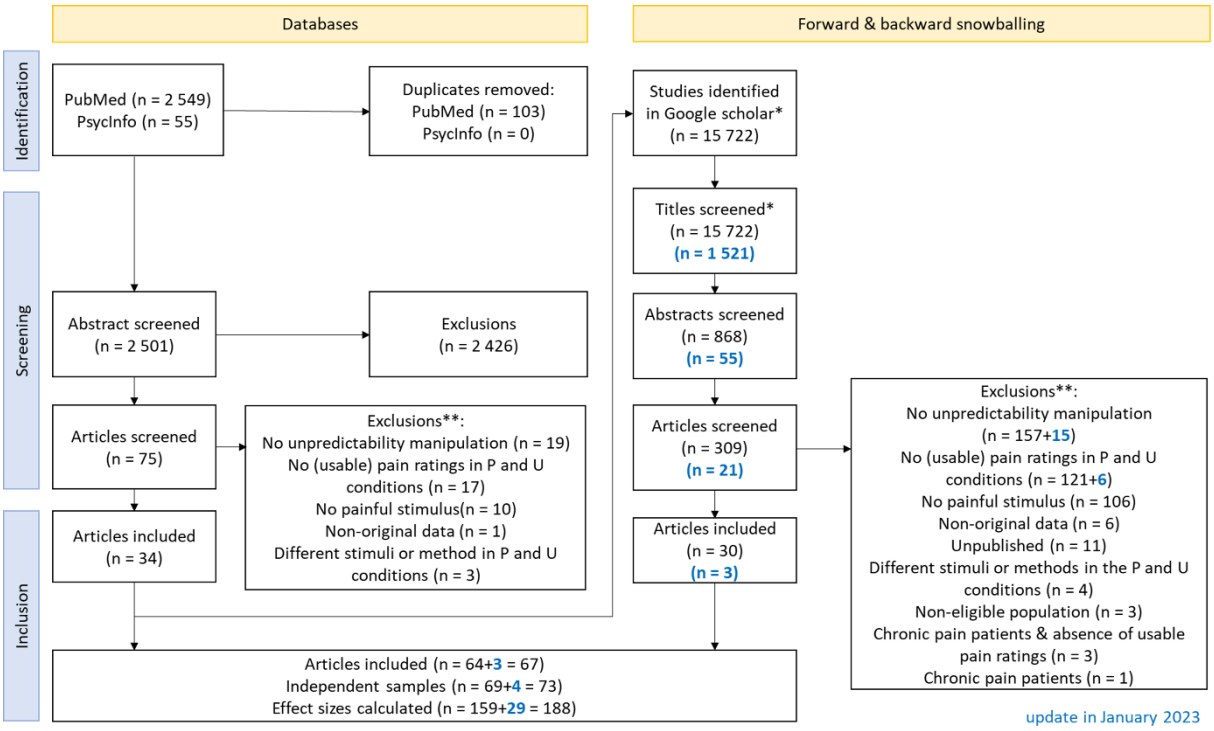

Fig 1. Flowchart of the literature screening procedure based on the PRISMA guidelines. The initial literature screening took place from November 2020 to May 2021. The numbers of titles, abstracts and articles evaluated during this stage are shown in black. The literature update took place in the first half of January 2023. The numbers of titles, abstracts and articles evaluated during the literature update are shown in blue. P: predictable, U: unpredictable. *: Including duplicates. **: some articles were excluded for several reasons. Articles sometimes contained results for different samples, hence the number of independent samples (73) slightly larger than the number of included articles (67). We favored the calculation of several effect sizes per study whenever they reflected different levels of the preregistered meta-regression moderators.

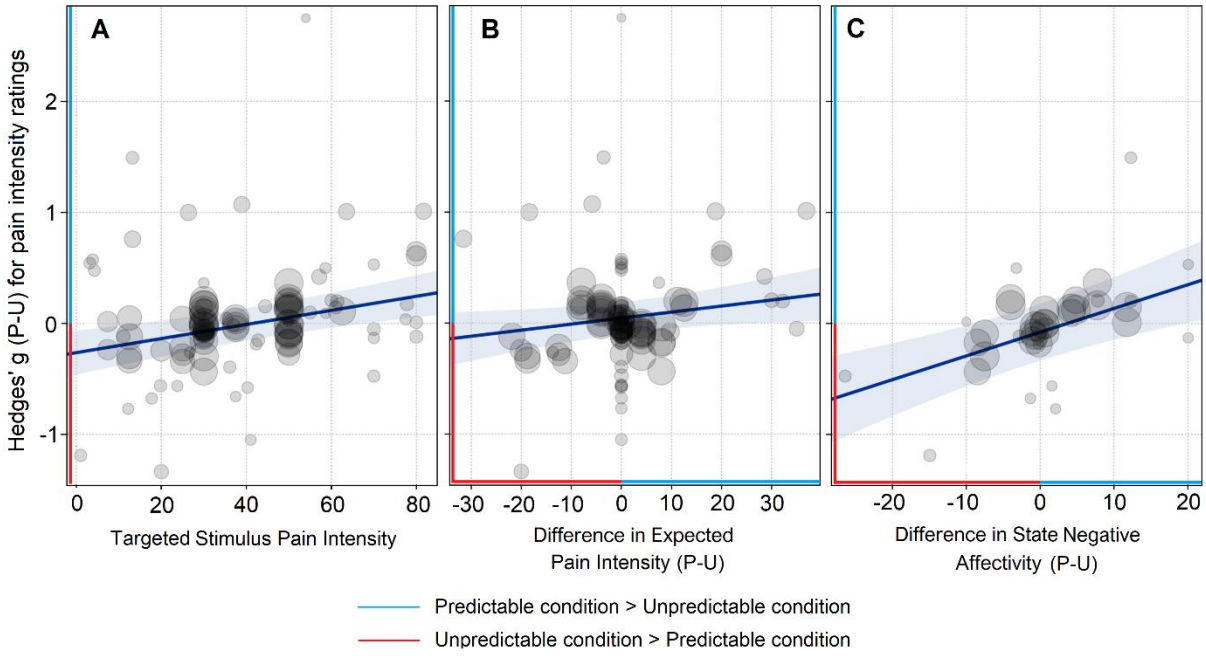

Fig 2. Effects of the significant moderators on the pain intensity rating effect sizes. The size of a dot represents its weight in the analyses, with larger dots having more weight. The plots include only the complete cases. The area of the 95% confidence interval of the regression line is shaded in grey. Positive Hedges' g (P-U) indicate that predictable stimuli were more painful, while negative Hedges' g (P-U) indicate that unpredictable stimuli were more painful. **A.** Targeted stimulus pain intensities were standardized such as 0 = no pain, 1 = pain threshold, 80 = very strong pain and 100 = extreme pain. The regression line suggests that unpredictability elicited slightly more pain for the less intense stimuli and that predictability elicited slightly more pain for the more intense stimuli. **B**. Positive differences on the x-axis indicate a higher expected pain intensity in the predictable than in the unpredictable condition. Negative differences indicate the opposite. Expected pain intensities ranged from 0 to 100 with 0 = no pain, 1 = pain threshold, 80 = very strong pain and 100 = extreme pain. The regression line shows that the condition (predictable or unpredictable) with higher expected pain intensity led to slightly more pain. **C.** Positive differences on the x-axis indicate more negative affectivity in the predictable than in the unpredictable condition. Negative differences indicate the opposite. The negativity affectivity scores from various scales and questionnaires were standardized to range from 0 to 100 such as 0 = lowest possible score and 100 = highest possible score. The condition which elicited more negative affectivity was also perceived more painful, regardless of (un)predictability of the condition.

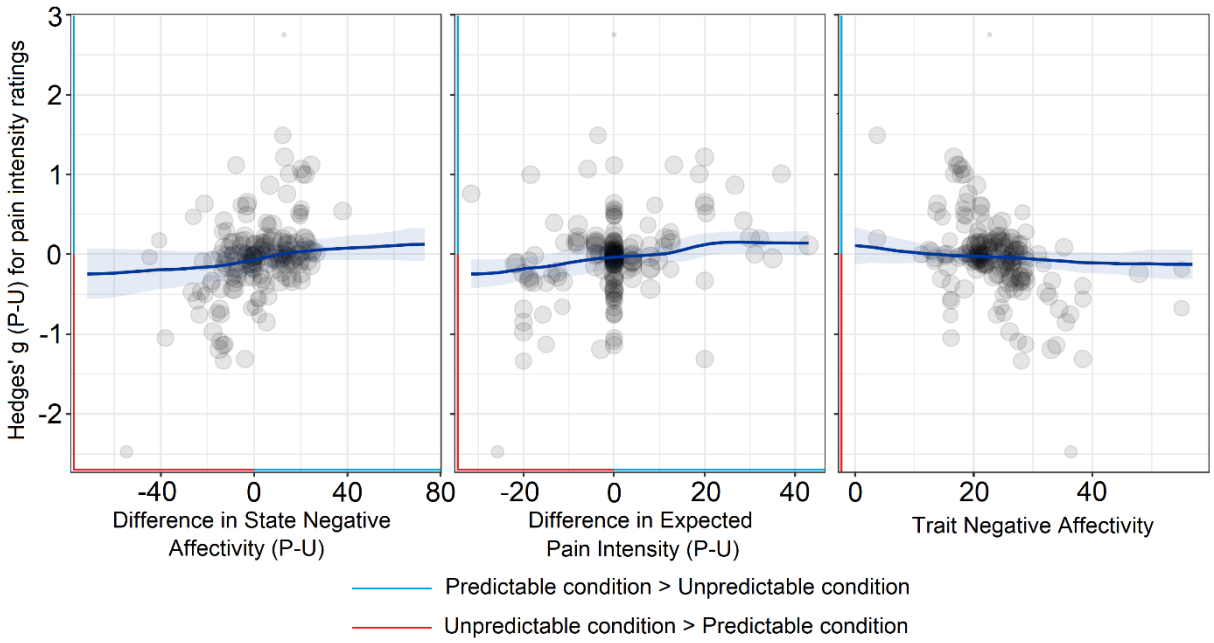

Fig 3. Partial dependence plots of the 3 most influential moderators on ratings of (un)predictable pain intensity (i.e Hedges' g (P-U) for pain intensity ratings). The plots were realized with the random forest analyses. They show the influence of each moderator marginalized over the 13 other moderators (see table 6). Each semi-transparent dot represents an observation (effect size). Larger dots represent more precise effect sizes. The blue lines represent the prediction for a new effect size (prediction pooled over the 51 imputed datasets). The shaded blue area surrounding the blue line represents the 95% prediction interval (standard error pooled over the 51 imputed datasets). Negative effect sizes indicate that the unpredictable condition was rated as more painful while positive effect sizes indicate that the predictable condition was rated as more painful. Negative differences in trait negative affectivity or differences in expected pain intensity indicate that the unpredictable condition elicited more negative affectivity or was associated with higher expectation. Positive differences indicate the opposite. Negative affectivity scores were standardized such as 0 = lowest possible score of a questionnaire and 100 = highest possible score of a questionnaire. As previously found with the complete cases meta-regressions, the condition which elicited more negative affectivity or more expected pain intensity seemed also more painful, regardless of the (un)predictability of the condition. We observed a tendency towards higher unpredictable as compared to predictable pain for the samples showing higher trait negative affectivity and vice versa for the samples showing lower trait negative affectivity. Any tendency was hardly distinguishable for the non-plotted moderators.