

Accepted Manuscript

Perceptual decision parameters and their relation to self-reported pain: a drift diffusion account

Jonas Zaman , Katja Wiech , Johan W.S. Vlaeyen

PII: S1526-5900(19)30752-7
DOI: <https://doi.org/10.1016/j.jpain.2019.06.009>
Reference: YJPAI 3765



To appear in: *Journal of Pain*

Received date: 15 March 2019
Revised date: 6 June 2019
Accepted date: 13 June 2019

Please cite this article as: Jonas Zaman , Katja Wiech , Johan W.S. Vlaeyen , Perceptual decision parameters and their relation to self-reported pain: a drift diffusion account, *Journal of Pain* (2019), doi: <https://doi.org/10.1016/j.jpain.2019.06.009>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Perceptual decision parameters and their relation to self-reported pain: a drift diffusion account

Running title

Decision parameters and self-reported pain

Jonas Zaman^{a,b}, Katja Wiech^{c,d} and Johan W.S. Vlaeyen^{a,e}

^aHealth Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Tiensestraat 102, box 3726, 3000 Leuven, Belgium

^bCenter for the Psychology of Learning and Experimental Psychopathology, Faculty of Psychology and Educational Sciences, KU Leuven, Tiensestraat 102, Box 3712, 3000 Leuven, Belgium

^cCentre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

^dNuffield Department of Clinical Neurosciences, Nuffield Division Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

^eExperimental Health Psychology, Maastricht University, P.O. Box 616, 6200 MD Maastricht Netherlands

Disclosures

JZ is a postdoctoral Research Fellow of the Research Foundation Flanders (FWO, 12P8619N). JV and JZ are supported by the “Asthenes” long-term structural funding—Methusalem grant (Meth/15/011) by the Flemish Government, Belgium. KW received funding from the MRC (UK). The authors have no conflict of interest to declare.

Corresponding author: Jonas Zaman, MSc, PhD, Health Psychology, University of Leuven,

Tiensestraat 102, 3080 Leuven, Belgium. Tel.: +32 16 37 31 97; Fax +32 16 3 26144

E-mail: jonas.zaman@kuleuven.be

Institutional URL: <http://ppw.kuleuven.be/home/english/research/ogp>

- Changes in pain ratings can be driven by at least two distinct mechanisms.
- Pain ratings related to the speed at which (in)noxious input was processed.
- Pain ratings increased the more the decision process was biased towards pain.

Abstract

Pain intensity ratings are subject to various cognitive modulations - yet the mechanisms underlying this influence are still not understood. In a conditioning protocol, pain-related expectations were induced through pairing predefined movements with a noxious or innocuous stimulus in either a predictable or unpredictable fashion. Healthy volunteers ($N = 37$) categorized the stimuli as either painful or non-painful and rated their perceived intensity. Using a Hierarchical Drift Diffusion model based on the categorization data, we found that an *a priori* decision-making bias evolved towards the expected sensations ($p < .001$). In particular, our findings suggest that differences in both the amount of decision-making bias ($p = .004$) and the speed sensory processing predict pain intensity ratings ($p < .001$). As such, changes in pain ratings could be based in either of these processes, which may require a different approach when targeted as part of psychological pain treatment.

Perspective

Changes in reported pain levels were linked to two distinct mechanisms, suggesting that increased pain reports could be attributed to either enhanced sensory processing or biased inferences. Our results might contribute to development of person-tailored treatments based on the identification of latent mechanisms using computational models.

Keywords: Hierarchical Drift Diffusion model, Pain ratings, Perception, Categorization, Decision-making

Introduction

One of the most profound developments in modern perception research has been the reformulation of perception as an inferential process. Instead of being a mere readout of sensory input, perception is now understood to be strongly determined by expectations that are generated based on prior knowledge^{5,10}. This critical influence of expectations also applies to the perception of pain. Expectations have been shown to affect pain perception in an experimental context^{3,8,15,33} and to predict pain treatment outcomes including long-term disability²⁴ and psychological functioning^{7,9,11} in clinical populations.

In the majority of these studies, the key indicator of pain modulatory effects has been a change in pain intensity ratings, most commonly acquired using either visual analogue or numerical rating scales. Although these measures undoubtedly capture changes in pain perception they are merely descriptive and allow for only limited insights into the mechanisms driving the modulation. To overcome this issue, computational models have been developed that use behavioral responses to test specific hypotheses on the cognitive mechanisms underlying perception. Drift diffusion models

(DDM), for instance, assume that a sequential sampling process underlies binary perceptual decisions. Perception is conceived as a statistical inference process in which noisy sensory input is accumulated over time. A perceptual “decision” is made as soon as a boundary is reached (see Fig. 1). Which response is given depends on whether either the upper or the lower boundary is reached¹⁸. In order to differentiate between various components of this decision process, these models integrate both response times and categorization accuracy (e.g., is the noxious input painful or not). Applying a hierarchical DDM³⁰ to decision data from healthy volunteers, we recently demonstrated that the expectation of high pain did not influence the speed at which noxious input is processed (reflected by the parameter drift rate). Rather, pain-related expectations influenced the decision process asymmetrically, such that less sensory input was needed to categorize the stimulation as painful, and more evidence was needed to categorize the stimulus as non-painful. This was shown by a shift in the starting point towards the expected response threshold²⁹. Similar approaches have successfully been applied to investigate the effects of stimulus salience^{17,18}, instructions emphasizing either speed or accuracy^{17,27} or fear learning³² on perceptual decision-making.

For methodological reasons, modelling approaches are primarily based on binary or multi-class categorizations (e.g., high-intensity versus low-intensity pain; pain versus no pain). How these computational modelling parameters map onto more commonly used pain intensity ratings remains to be elucidated. It seems reasonable to assume that enhanced sensory processing of noxious input, for instance, or a bias to decide whether sensory input was painful translates into an amplified perception of pain, and increased pain intensity ratings. However, without direct evidence this prediction remains speculative.

Here, a conditioning protocol was adopted using movement-generated proprioceptive stimuli as conditioned stimuli (CSs), and (noxious) electrocutaneous stimuli as unconditioned stimuli (US). In the predictable condition (P), the noxious US was always presented during the execution of a predefined arm movement (CS+), whereas a second movement (CS-) was always followed by an innocuous US. An unpredictable condition where both USs could be presented during the execution of arm movements, served as control condition. Upon US presentation, participants categorized the US as either painful or not, and subsequently rated its intensity using a visual analog scale (VAS). Response time and accuracy data were used to estimate the different parameters of the decision-making process according to a Hierarchical Drift Diffusion model²⁵ (for more details see *Drift Diffusion model*). We hypothesized that the model parameter reflecting the expectancy-related bias would correspond to the reported stimulus intensity. A bias towards pain was expected to lead to higher pain ratings, whereas a bias favoring no pain should be reflected in lower ratings.

Material and Methods

Participants

Of the 44 healthy volunteers who participated, data of seven participants was not available or could not be used due to technical problems (i.e., software problems or malfunctioning stimulation device), resulting in 37 participants who were included in the final analyses (28 females, mean age: 21.84 ± 4.48). Comparable or smaller sample sizes have been adopted in previous research with similar protocols^{29,32,34}. Volunteers were recruited through local advertisement boards and were paid 15 euros. All participants provided their written informed consent. Exclusion criteria based on self-report were a history of cardiac, breathing or cardiovascular disorders, neurological disorders, chronic pain and psychiatric disorders, pregnancy, hearing difficulties, acute pain, use of recreational drugs, ongoing recovering from severe physical trauma, advice from general practitioner to avoid stress, any type of electronic implant (e.g., pacemaker), pain or discomfort located at the wrist, arm or shoulder. The study was approved by the Medical Ethical Committee of the University Hospitals Leuven, Belgium (Reg. Nr S56566).

--- please insert Fig. 1 about here ---

Electrocutaneous stimulation

The electrocutaneous stimuli were applied at the distal end of the humerus of the non-dominant arm using a commercially available electrocutaneous stimulation device (Constant Current Stimulator, model DS5; Digitimer®, Hertfordshire, UK) delivering a 2 ms monopolar square waveform pulse via two surface electrodes (V91-01, 8mm, Coulbourn®) filled with K-Y gel (Johnson & Johnson, New Brunswick, NJ). Stimulation levels were determined for each individual using the Ascending Methods of Limits approach³¹. The stimulation intensity was gradually increased until a score of 8 was reached on a visual analog scale (VAS), with the following labels: 0= no sensation, 1= weak sensation, 2= clear sensation, 6= faint pain, 7= painful, 8= strong pain but tolerable, 10= extreme, intolerable pain, which were shown throughout the experiment. During this procedure two stimulation levels were determined, an innocuous stimulus (US_i) of a low intensity (corresponding to VAS-score of 3) and a noxious stimulus (US_N , corresponding to a VAS-score of 8). Mean intensities for US_i and US_N , were 28.86 mA (± 9.09) and 66.93 mA (± 15.62), respectively. Both stimulation intensities were delivered through the same pair of electrodes. Following a practice phase, all stimuli were presented once and recalibrated if indicated by the VAS ratings provided.

--- please insert Fig. 2 about here ---

Proprioceptive conditioning paradigm

Arm extensions were executed with the Haptic Master (HM), a 3-degrees of freedom, force-controlled haptic interface (MOOG®, The Netherlands) enabling movement of a robotic arm along the x, y and z-axis, programmed to guide movements. These movements generated proprioceptive stimuli that acted as CSs. Participants operated the robotic arm with their non-dominant hand. The HM restricted movement directions to the horizontal plane, but did not exert any force. Four different movements (two to the participant's left side and two to the right side) were programmed with varying angles (left: 22.5°, 77.5°; right: 112.5°, 157.5°) in the horizontal (x-z) plane while distance of movement and starting point were identical (Fig. 2). Movements to the left and right were randomly allocated to the predictable and unpredictable condition, respectively. Within the predictable condition, one of two orientations served as the CS+ (i.e., paired with the noxious stimulus US_N), whereas the other served as the CS- (i.e., paired with the innocuous stimulus US_I). CS+ allocation was counterbalanced across subjects. Within the unpredictable condition, the US_N could occur during each of the two movements (labelled CS_{U1} and CS_{U2}) in 50% of the trials, whereas in the remaining trials US_I was presented.

Procedure

Upon arrival, participants were briefed and informed consent was obtained. Participants were seated in front of the HM, so that the robotic arm was located approximately 20cm away. Electrodes were attached and the dominant hand was positioned on the response box. The experiment consisted of a practice phase, and four blocks [2 predictable (P) and 2 unpredictable blocks (U)] in pseudo-randomized order. The following block orders were used: P-U-U-P, U-P-P-U, U-P-U-P and P-U-P-U. The first P and U block comprised an acquisition phase where subjects learned the CS-US contingencies and a test phase (that was identical to the acquisition phase apart from the number of trials). The remaining two blocks only consisted of a test phase. Only data from the test phase will be included in the analyses as the acquisition phase served as a learning phase. Depending on the condition, the background of the screen changed from black (practice) to either blue or orange to indicate the type of block. Allocation of colors to the different conditions was counterbalanced across participants.

Protocol

Instructions emphasized both speed and accuracy to categorize the USs as either painful or non-painful by pressing one of two response buttons with the dominant hand. Response options were randomly allocated to the two buttons across participants. A trial started with the on-screen presentation of the word "START" (1.5s) that cued participants to grab the HM and initiate the

movement (see Fig. 2). Movement execution continued until the word “STOP” instructed participants to remove their hand from the HM, which automatically moved back to the start position. The screen remained black for 2s after which a VAS scale appeared for a fixed duration of 5.5s to obtain pain intensity ratings. Note that participants were unaware of the movement direction until they actually exerted force and discovered in which direction they could move as no visual cues were presented (to ensure that the movement and not visual information served as CS). To help participants pace their movement to a 6s duration, a timer incrementing in 1-sec steps was displayed on the screen. The extension trajectories were divided into two segments relative to the starting point, the first segment at 33% of the total distance (first boundary) and the second segment at 66% of the distance (second boundary) (Fig. 2). Eyeblink startle probes were presented when the first boundary was crossed, while the electrocutaneous stimuli were presented upon crossing of the second boundary. If the first boundary was reached within less than two seconds, the warning “Too fast” appeared at the end of the trial, and the trial returned to the trial pool to be repeated.

During practice, participants performed twelve arm extensions (with different angles, 45° and 135°, as the CS angles) during which either the US_I or US_N was applied (six times each). Acoustic startle probes were presented on each trial to allow for habituation. In a predictable block, acquisition comprised 24 trials with 12 CS+ and 12 CS- trials whereas in an unpredictable block 12 CS_{U1} and 12 CS_{U2} trials were presented. A startle probe was presented in 50% of the trials. The test phase was identical to the practice phase, except that 16 trials were presented per CS and that a startle probe was presented in 25% of the trials. At the end of each phase participants provided ratings of US-expectancy for each of the movements (‘0’= no expectation of pain, ‘100’= expectation of pain), fear (‘0’= not fearful, ‘100’= very fearful), unpleasantness (‘0’= not unpleasant, ‘100’= very unpleasant), and arousal (‘0’= not tensed, ‘100’= very tensed) by moving a slider on a VAS scale using two buttons which shifted the slider to the left and right. The questions were presented in a randomized order.

Eyeblink startle responses

The startle eyeblink reflex is a frequently adopted psychophysiological index of defensive mobilization, and was used to infer differences in fear learning between the CSs^{2,13} as potentiation of the startle eyeblink reflex has been found during predictable and unpredictable pain contexts compared to a safe context^{14,21}. Orbicularis oculi electromyographic activity (EMG) was recorded using three disposable trimmed Ag/AgCl electrodes (H124SG, 24 mm, Covidien®), according to the guidelines of Blumenthal and colleagues¹. The skin was abraded with a mild abrasive cream (Inecto). The raw signal was amplified (v75-04, Coulbourn isolated bioamplifier®) with a 13Hz high pass and 500Hz low pass bandpass filter and rectified and smoothed with a time constant of 20ms (V76-24, Coulbourn Integrator®). EMG sampled at 1000Hz was recorded from 200ms prior to probe onset

until 800ms after probe onset. Startle eye blink amplitudes were calculated by subtracting the mean baseline value (0-20 ms after probe onset) from the peak value found in the 21-175 ms time window after startle probe onset. Data was visually inspected (offline) for artifacts (e.g., spontaneous blinks) and rejected if necessary. Startle data from one participant was excluded due to excessive noise. Five participants were labeled non-responders as more than 50% of their startle responses were classified as non-response and omitted from startle analyses. To reduce inter-individual variation, startle amplitudes were transformed into T-scores and mean startle amplitudes were calculated per phase and CS. None of the reported means were based on fewer than four observations.

Drift Diffusion model

Drift diffusion models operationalize binary decision-making as a sequential sampling process where evidence sampled from sensory input accumulates in favor of one of the decision outcomes (see Fig. 1). Through combination of categorization accuracy and response time distributions various parameters of this process are estimated^{18,30}. We investigated the binary decision to categorize a stimulus as painful or not painful (pain vs. no pain). Upon stimulus presentation the information accumulation process starts in-between two boundaries. One boundary represents the pain response, the other boundary represents the no pain response. The relative distance between the starting point (parameter z) and the two response boundaries can vary depending on the expectation of the individual. For example, the starting point will be closer to the pain boundary when a painful stimulus is expected which favors the expected percept. The rate by which information accumulates is captured by the parameter drift rate (v), with larger drift rates indicating faster evidence accumulation. The distance between the two boundaries reflects decision conservativeness, captured by the parameter boundary separation (a). When boundaries are close, less sensory evidence accumulation is needed to make a decision compared to when boundary separation is large. Finally, these models also include a non-decision parameter called 'non-decision time' (T_{er}) that comprises processes that are unrelated to decision-making such as stimulus encoding and response execution.

A Python-based algorithm (http://ski.clps.brown.edu/hddm_docs/; Wiecki et al.³⁰) was used to estimate a Hierarchical Drift Diffusion model as hierarchical models require fewer data points per participant compared to the traditional diffusion models as parameters are drawn from a group distribution²⁵. Parameter estimation was based on the data from the test phases comprising in total 128 trials per participant. The best fitting model was selected using the Deviance Information Criteria (DIC). The preferred model was set up such that drift rate depended upon stimulus features (US_N vs.

US_i) and condition (predictable vs. unpredictable), and boundary separation and starting point differed between the CS+, CS- and CS_u. Non-decision time was kept fixed across conditions or stimuli although intertrial variability was allowed²⁶. Markov chain Monte-Carlo (MCMC) sampling methods were used to generate probability distributions for the parameters – the ‘posterior distributions’. We opted to use non-informative priors, which are uniform distributions with equal probabilities across a range of parameter values. In total, 40 000 samples were generated and the first 5 000 were discarded because initial samples are considered unreliable due to random selection of initial values, and thinned by a factor 2. The HDDM convergence diagnostics (all R-hats < 1.01) indicated that MCMC convergence was reached. Based on the assumption that outliers were due to other processes of no interest here¹⁹, RTs ± 2 SD from each participant’s mean and RTs below 200ms were removed (on average 3.9% of each participant’s data, SD of RTs = 1.72%) prior to model fitting.

Data analyses

Startle eye blink responses and self-report data were analyzed with a one-way repeated measures ANOVA with CS Type (CS+, CS_u / CS-) as within-subject factor. Data from acquisition and test blocks were combined for startle and self-report data. Greenhouse-Geiser corrections were applied for violations of sphericity when appropriate. Uncorrected degrees of freedom and corrected p-values are reported together with ϵ . Partial squared eta (η_p^2) effect sizes are reported for the ANOVAs, with small, medium, and large effects corresponding to values of 0.0099, 0.0588, and 0.1379, according to Cohen⁶.

A linear mixed model (LMM) was used to analyze trial-by-trial pain intensity ratings with the factors Stimulus (US_i vs. US_N), Categorization (pain vs. no pain), Condition (predictable vs. unpredictable) and Trial, their interactions (i.e., Stimulus \times Categorization, Stimulus \times Condition, Categorization \times Condition and Categorization \times Condition \times Stimulus), and Participant as a random intercept (for model parameter estimates see *supplemental information*). Only data from the test phase was included as the acquisition phase served as a learning phase. Standardized effect sizes (δ_w) and corresponding 95% CIs were calculated according to Lai and Kwok (2016)¹². Degrees of freedom were rounded to integers as they were estimated using a Satterthwaite approximation²⁰.

The estimated individual drift diffusion parameters were entered into repeated measures ANOVA’s with Trial Type (CS_u/CS+/CS-) as within-subject factor for the parameters ‘starting point’ and ‘boundary separation’. For the parameter ‘drift rate’, the within-subject factors Condition (Pred/Upred), and Stimulus (US_i/US_N), as well as their interaction were included.

In order to investigate the relationship between parameter estimates and pain ratings, mean pain ratings (per condition and stimulus) were entered into separate mixed models for each model

parameter. In comparison to simple correlation analysis, this approach allowed us to quantify the extent to which variations in pain rating reflect processes captured by the model parameters while controlling for the influence of Stimulus and Condition (for full model details see *supplemental information*). All post-hoc contrasts were tested two-tailed and corrected for multiple testing using the stepdown Bonferroni correction. All data analyses were performed using SPSS 20.

--- please insert Table 1 about here ---

Results

Self-reports

There was a main effect of CS type on self-reported fear [$F(2,72) = 30.085, p < .001, \eta^2_p = .445, \varepsilon = .629$], tension [$F(2,72) = 26.319, p < .001, \eta^2_p = .422, \varepsilon = .625$], unpleasantness [$F(2,72) = 22.478, p < .001, \eta^2_p = .384, \varepsilon = .619$] and US-expectancy ratings [$F(2,72) = 33.756, p < .001, \eta^2_p = .484, \varepsilon = .601$]. The highest self-reported ratings were found for the CS+ with intermediate rating for the CS_u and the lowest ratings for the CS- (all p 's $< .001$) (see Table 1).

Startle eye blink responses

The main effect of CS type failed to reach significance [$F(2,60) = 2.851, p = .066, \eta^2_p = .066$]. None of the post hoc test survived the Bonferroni correction (all p 's > 0.09) albeit a trend for higher amplitudes during both the CS+ and the CS_u compared to the CS- emerged (see Table 1).

Pain ratings

Mixed model analyses revealed a main effect of Trial [$F(1, 4670) = 49.03, p < .001, \delta_w = 0.015, 95\% \text{ CI} = [0.01, 0.02]$] as ratings increased slightly over the course of the experiment. As expected, ratings were significantly higher when a US_N was presented [main effect of Stimulus: $F(1, 4675.36) = 2587.35, p < .001, \delta_w = -5.154, 95\% \text{ CI} = [-6.42, -3.89]$] or when the stimulus was categorized as painful [main effect of Categorization: $F(1, 4677.24) = 787.72, p < .001, \delta_w = -2.639, 95\% \text{ CI} = [-3.31, -1.96]$] (see Fig. 3A). There was no main effect of Condition [$F(1, 4672.53) = 3.62, p = .057, \delta_w = -0.077, 95\% \text{ CI} = [-0.19, 0.04]$]. There was a significant Stimulus \times Condition interaction: [$F(1, 4672.45) = 16.43, p < .001, \delta_w = -0.941, 95\% \text{ CI} = [0.36, 1.52]$]. The presentation of US_N resulted in higher pain ratings in the predictable compared to the unpredictable condition [$t(4673.30) = 1.97, p = .050$] whereas US_I were rated as more intense in the unpredictable condition [$t(4673.30) = 3.64, p < .001$]. Furthermore, there was a significant Stimulus \times Categorization interaction [$F(1, 4678.07) = 13.64, p < .001, \delta_w = 0.895, 95\% \text{ CI} = [0.35, 1.44]$] as the categorization of a stimulus as painful led to higher pain ratings when the presented stimulus was the US_N compared to the US_I [$t(4675.70) = 33.27, p < .001$]. Last,

there was a significant Categorization \times Condition interaction [$F(1, 4673.09) = 7.46, p = .006, \hat{\delta}_w = -0.216, 95\% \text{ CI} = [-0.61, 0.17]$]. When comparing the predictable with the unpredictable condition, pain ratings following the categorization of a stimulus as non-painful did not differ between conditions [$t(4671.14) = 0.78, p = .439$], whereas they were relative higher following the categorization of a stimulus as painful in the unpredictable compared to the predictable condition [$t(4673.62) = 2.80, p = .005$] (for full model see Supplemental information).

--- please insert Fig. 3 about here ---

Decision-making

Starting point

As expected, the starting point was higher for the CS+ as compared to CS_u [$t(36) = 4.490, p < .001$]. Furthermore, the starting point during the CS- was lower than the one for the CS_u [$t(36) = -4.218, p < .001$] [main effect of Trial Type: $F(2, 72) = 28.824, p < .001, \epsilon = .806, \eta^2_p = .445$] (see Fig. 3C).

Drift rate

Drift rates for the US_i were significantly higher than those for the US_N [main effect Stimulus: $F(1, 36) = 91.695, p < .001, \eta^2_p = .718$] and were higher when stimuli were presented in a predictable manner compared to the unpredictable condition [main effect Condition: $F(1, 36) = 5.386, p = .026, \eta^2_p = .130$]. However, this effect was driven by a Stimulus \times Condition interaction [$F(1, 36) = 17.033, p < .001, \eta^2_p = .321$], as drift rates for US_i in the predictable condition were significantly higher compared to those in the unpredictable condition [$t(36) = 3.725, p = .001$]. The drift rate of US_N was similar in both conditions ($p = .163$) (see Fig. 3D).

Boundary separation

We found a main effect of Trial Type for boundary separation [$F(2, 72) = 46.486, p < .001, \eta^2_p = .564$]. The largest distance between the two thresholds was found during the CS- compared to the CS_u [$t(36) = 3.712, p = .001$], and with the smallest distance for the CS+ compared to the CS_u [$t(36) = -6.378, p < .001$] (see Fig. 3E).

Decision-making and pain ratings

In the final step of our analysis, we investigated the degree to which variations in drift diffusion parameter estimates scaled with pain intensity ratings while controlling for Stimulus and Condition effects on pain ratings. Our data show a significant association between the Starting Point and pain ratings [main effect of Starting Point: $F(1, 127.78) = 8.704, p = .004, \hat{\delta}_w = 4.90, 95\% \text{ CI} = [1.60, 8.20]$] with higher pain ratings the nearer the Starting Point was located towards the (upper) pain boundary

(Fig. 4A). Second, we found an overall effect of Drift Rate on pain ratings [$F(1, 113.44) = 8.368, p = .004, \hat{\delta}_w = 0.78, 95\% \text{ CI} = [0.73, 1.08]$] which depended on the Stimulus [Drift rate \times Stimulus interaction: $F(1, 114.31) = 35.937, p < .001, \hat{\delta}_w = -0.94, 95\% \text{ CI} = [-1.00, -0.61]$]. More specifically, higher Drift Rates led to lower pain ratings for innocuous stimuli [$US_I: F(1, 49.54) = 12.051, p = .001$] and to higher pain ratings when a noxious stimulus (US_N) was presented [$F(1, 62.04) = 12.132, p = .001$; Fig. 4B]. The relationship between Boundary Separation and pain ratings was not significant ($p = .265$; Fig. 4C).

--- please insert Fig. 4 about here ---

Discussion

For decades, pain intensity ratings have been the primary outcome variable in studies investigating the influence of expectations on pain perception. A more recent stream of research, however, uses indices of dichotomous decisions (e.g. response times and accuracy of low-intensity vs. high-intensity pain categorization) to characterize mechanisms underlying the perception of pain as an inferential process^{4,22,23,28,29,32,34}. Because both lines of research have been kept relatively separate, it remains unclear how changes in pain ratings map onto computational model parameters, which renders relating findings from both research lines difficult. Here, we acquired pain intensity ratings and estimated model parameters within the same experiment to explore the relationship between both outcomes. Our data provide evidence that pain ratings can be driven by at least two distinct mechanisms as ratings relate both to the speed at which (in)noxious input is processed (i.e., in drift rate) as well as to the extent that a bias towards pain is embedded in the decision process.

Our finding that prior knowledge about the expected stimulation intensity leads to more extreme stimulus intensity ratings has been reported before. In a study by Brown and colleagues (2008) innocuous stimuli were rated as less intense and noxious stimuli as more intense when they were preceded by a visual cue that correctly predicted the intensity of the subsequent stimulation³. Such findings are in line with contemporary models of perception that predict more extreme rating when (correct) expectations guide the analysis of incoming sensory information compared to an unpredictable context where expectations evolve over several stimulus presentations by integrating all available information (i.e., noxious as well as innocuous stimuli) into an average representation¹⁶.

Computational modelling allows for a more in-depth exploration of the mechanisms driving this influence of prior information. In line with previous studies using a drift diffusion approach^{29,32}, we found that the expectation of (no) pain biased the decision process (a shift in starting point), and influenced the speed at which incoming sensory information is processed (a change in drift rate). Unexpectedly, we also found differences in the required amount of sensory evidence to make a

decision (reflected by the parameter boundary separation) between our different pain conditions (Fig. 3). However, of these three model parameters, only starting point and drift rate were directly associated with stimulus intensity ratings (Fig. 4).

The expectation of pain induced a shift in starting point towards the pain decision-threshold (or *a priori* decision-making bias) indicating that the decision process favored the interpretation of incoming information as painful (Fig. 3C). Likewise, the expectation of an innocuous stimulus in the CS- condition shifted the starting point towards the no-pain boundary. However, in both cases this was only true relative to the unpredictable condition. As hypothesized, the starting point for the unpredictable condition lay between those for the CS+ and CS-. But in all three conditions the prior was located above the neutral starting point of 0.5, indicating that even in the unpredictable and the CS- conditions in which no noxious stimulus was applied, participants' starting point was located more proximal to the pain boundary. Such finding could be reflective of different processes. *First*, more salient noxious stimulation could have caused an offset effect in which pain was expected in all conditions, although to a larger degree in the CS+ condition and less so in the CS_u and CS- condition. *Second*, learning itself might have been compromised and have led to false predictions. The design required the participants to differentiate between both stimulation intensities throughout the experiment. If the stimulation had become indistinguishable (e.g., due to sensitization following repeated stimulation) participants might have perceived a stimulation as painful although it was intended to be non-painful. As a consequence, participants would have learned an incorrect representation of contingencies. However, as shown in Fig. 3B, participants were very well able to correctly categorize the US in the CS- condition, which renders incorrect contingency learning an unlikely explanation. When participants developed an *a priori* decision-making bias (indicated by a shift in starting point) favoring the interpretation of sensory input as painful, they also rated stimuli as more painful (Fig. 4A). This positive relationship with intensity ratings was found for both noxious and innocuous sensory input. As the position of the starting point is established when the CS is presented (i.e., *prior* to the arrival of any sensory input), this finding is a strong indicator for a *causal* relationship between a change in starting point and the subsequent change in perception in the sense that biased decision-making can drive increased pain reports.

Processing speed of the sensory input was the second model parameter that differed between conditions and showed a direct relationship with pain intensity ratings. Higher drift rates were found in the predictable condition, but mainly when innocuous stimuli were applied (Fig. 3D). Higher drift rates for innocuous stimuli relative to noxious sensory input have been reported previously^{29,32}. However, that higher processing rates occur in the predictable condition is at odds with the reported increase in drift rate when a high-intensity stimulus was unexpectedly applied²⁹. Typically, higher

drift rates are observed for stimuli with a high signal-to-noise ratio^{17,18,27}. Given that our study used fixed stimulation intensities, any variation in drift rate should be the result of differences in stimulus processing rather than differences in stimulus quality. Furthermore, our finding that the speed of sensory processing is related to more extreme ratings for both noxious and innocuous stimuli (Fig. 4B) is in line with Bayesian perception models, predicting that the quality of sensory processing determines the width of the stimulus likelihood and subsequently its impact upon the perception of a stimulus (i.e., the posterior)¹⁶.

Boundary separation as the third model parameter differed between conditions, but was not directly related to pain intensity ratings. As shown in Fig. 3E, boundary separation varied depending on the type of CS. Participants required less evidence to make a perceptual decision (i.e., low boundary separation) when noxious stimuli were applied (i.e., CS_u and CS+), and when the stimuli were predictable (CS+). As this parameter reflects the level of conservatism in decision-making, the finding suggests that participants were prepared to swiftly categorize a stimulus when “pain” (vs. no pain) was a potential outcome, irrespective of the correctness of the decision. This choice could reflect a ‘better-safe-than-sorry’ strategy that would tolerate miscategorization of innocuous stimuli as painful in order to maximize safety. This algorithm considers time as a relevant decision factor because failing to detect potentially harmful input early enough could be costly. In a context where pain is unlikely, however, (decision) time is less critical and is therefore better invested in the correctness of the categorization. Boundary distance did not scale with the perceived stimulus intensity (Figure 4C). Instead, identical intensity ratings were reported with narrow as well as wider boundaries when noxious or innocuous stimuli were applied. This finding is not unexpected because in contrast to the two previous types of bias, boundary separation does not directly favour one of the two categories. Both boundaries are conceptualized as equidistant from the centerline – so the same amount of evidence is required to reach either of them. Any change towards more liberal or conservative decision-making would therefore affect both outcomes equally.

Taken together, the finding that biased decision-making and altered sensory processing can result in the same behavioral phenotype illustrates how computational approaches can add value to the exploration of processes underlying the influence of expectations on pain perception. It seems reasonable to assume that both processes require different intervention strategies when targeted during psychological pain treatment. The differentiation of underlying processes could therefore guide treatment decisions to ensure that interventions specifically address the process that drives expectancy-related pain amplification in the individual. In order to move this approach closer to clinical application, further studies are needed to explore to which extent our findings apply to other

pain levels, other types of perceptual categorization (e.g., low vs. high intensity pain), other stimulus modalities and different chronic pain populations.

Author contribution

JZ developed the study concept. All authors contributed to the study design. JZ collected the data and performed the data analysis. JZ and KW drafted the manuscript, and KW and JWSV provided critical revisions. All authors approved the final version of the manuscript for submission.

ACCEPTED MANUSCRIPT

References

1. Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp O V, van Boxtel A: Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology* 42:1–15, 2005.
2. Bradley MM, Lang PJ: Affective reactions to acoustic stimuli. *Psychophysiology* 37:204–15, 2000.
3. Brown CA, Seymour B, Boyle Y, El-Deredy W, Jones AKP: Modulation of pain ratings by expectation and uncertainty: Behavioral characteristics and anticipatory neural correlates. *Pain* 135:240–50, 2008.
4. Brown CA, Seymour B, El-Deredy W, Jones AKP: Confidence in beliefs about pain predicts expectancy effects on pain perception and anticipatory processing in right anterior insula. *Pain* 139:324–32, 2008.
5. Clark A: Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci* 36:181–204, 2013.
6. Cohen J: The statistical power of abnormal-social psychological research: A review. *J Abnorm Soc Psychol* 65:145–53, 1962.
7. Cormier S, Lavigne GL, Choinière M, Rainville P: Expectations predict chronic pain treatment outcomes. *Pain* 157:329–38, 2016.
8. Corsi N, Colloca L: Placebo and Nocebo Effects: The Advantage of Measuring Expectations and Psychological Factors. *Front Psychol* 8:, 2017.
9. Foster NE, Thomas E, Hill JC, Hay EM: The relationship between patient and practitioner expectations and preferences and clinical outcomes in a trial of exercise and acupuncture for knee osteoarthritis. *Eur J Pain* 14:402–9, 2010.
10. Friston K, Kiebel S: Predictive coding under the free-energy principle. *Philos Trans R Soc B Biol Sci* 364:1211–21, 2009.
11. Hoffmann TC, Del Mar CB, Strong J, Mai J: Patients' expectations of acute low back pain management: implications for evidence uptake. *BMC Fam Pract* 14:7, 2013.
12. Lai MHC, Kwok OM: Estimating Standardized Effect Sizes for Two- and Three-Level Partially Nested Data. *Multivariate Behav Res Taylor & Francis*; 51:740–56, 2016.

13. Lang PJ, Davis M, Ohman A: Fear and anxiety: animal models and human cognitive psychophysiology. *J Affect Disord* 61:137–59, 2000.
14. Meulders A, Vansteenwegen D, Vlaeyen JWS: The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. *Pain* 152:2460–9, 2011.
15. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, Vase L: The magnitude of placebo effects in pain: a meta-analysis. *Pain* 155:1426–34, 2014.
16. Petzschner FH, Glasauer S, Stephan KE: A Bayesian perspective on magnitude estimation. *Trends Cogn Sci* 19:285–93, 2015.
17. Ratcliff R: A diffusion model account of response time and accuracy in a brightness discrimination task: fitting real data and failing to fit fake but plausible data. *Psychon Bull Rev* 9:278–91, 2002.
18. Ratcliff R, McKoon G: The diffusion decision model: theory and data for two-choice decision tasks. *Neural Comput* 20:873–922, 2008.
19. Ratcliff R, Tuerlinckx F: Estimating parameters of the diffusion model: approaches to dealing with contaminant reaction times and parameter variability. *Psychon Bull Rev* 9:438–81, 2002.
20. Satterthwaite FE: An approximate distribution of estimates of variance components. *Biometrics* 2:110–4, 1946.
21. Schmitz A, Grillon C: Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nat Protoc Nature Publishing Group*; 7:527–32, 2012.
22. Seymour B, O’Doherty JP, Dayan P, Koltzenburg M, Jones AK, Dolan RJ, Friston KJ, Frackowiak RS: Temporal difference models describe higher-order learning in humans. *Nature* 429:664–7, 2004.
23. Seymour B, O’Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, Dolan R: Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat Neurosci* 8:1234–40, 2005.
24. Turner JA, Franklin G, Fulton-Kehoe D, Sheppard L, Wickizer TM, Wu R, Gluck J V, Egan K: Worker recovery expectations and fear-avoidance predict work disability in a population-based workers’ compensation back pain sample. *Spine (Phila Pa 1976)* 31:682–9, 2006.

25. Vandekerckhove J, Tuerlinckx F, Lee MD: Hierarchical diffusion models for two-choice response times. *Psychol Methods* 16:44–62, 2011.
26. Verdonck S, Tuerlinckx F: Factoring out nondecision time in choice reaction time data: Theory and implications. *Psychol Rev* 123:208–18, 2016.
27. Voss A, Rothermund K, Voss J: Interpreting the parameters of the diffusion model: an empirical validation. *Mem Cognit* 32:1206–20, 2004.
28. Wiech K: Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science (80-)* 354:584–7, 2016.
29. Wiech K, Vandekerckhove J, Zaman J, Tuerlinckx F, Vlaeyen JWSJWS, Tracey I: Influence of prior information on pain involves biased perceptual decision-making. *Curr Biol* 24:R679-81, 2014.
30. Wiecki T V, Sofer I, Frank MJ: HDDM: Hierarchical Bayesian estimation of the Drift-Diffusion Model in Python. *Front Neuroinform* 7:14, 2013.
31. Yarnitsky D, Sprecher E, Zaslansky R, Hemli J a: Heat pain thresholds: normative data and repeatability. *Pain* 60:329–32, 1995.
32. Zaman J, Madden VJ, Iven J, Wiech K, Weltens N, Ly HG, Vlaeyen JWSJWS, Van Oudenhove L, Van Diest I: Biased Intensity Judgements of Visceral Sensations After Learning to Fear Visceral Stimuli: A Drift Diffusion Approach. *J Pain* 18:1197–208, 2017.
33. Zaman J, Vanpaemel W, Aelbrecht C, Tuerlinckx F, Vlaeyen JWS: Biased pain reports through vicarious information: A computational approach to investigate the role of uncertainty. *Cognition* 169:54–60, 2017.
34. Zaman J, Wiech K, Claes N, Van Oudenhove L, Van Diest I, Vlaeyen JWS: The influence of pain-related expectations on intensity perception of non-painful somatosensory stimuli. *Psychosom Med* :1, 2018.

Figure Legends

Fig. 1. Schematic representation of a drift diffusion process. The response time (RT) distributions with a red contour represent errors (i.e., the categorization of an innocuous stimulus as painful, or a noxious stimulus as not painful). The decision process consists of the noisy accumulation of evidence (red dotted lines) until one of two decision thresholds is reached and a response is executed. The signal-to-noise ratio is reflected in the drift rate (v) as it represents the average speed of information accumulation. The degree of decision conservativeness is reflected by boundary separation (a) as the distance between the orthogonal decision thresholds can vary, thereby increasing or decreasing the required amount of evidence in order to make a decision. The starting point (z) of the accumulation process relative to the two decision thresholds can vary reflecting prior knowledge [i.e., an a priori bias]. Final, a non-decision component (T_{er}) comprises the time required for stimulus encoding and response execution.

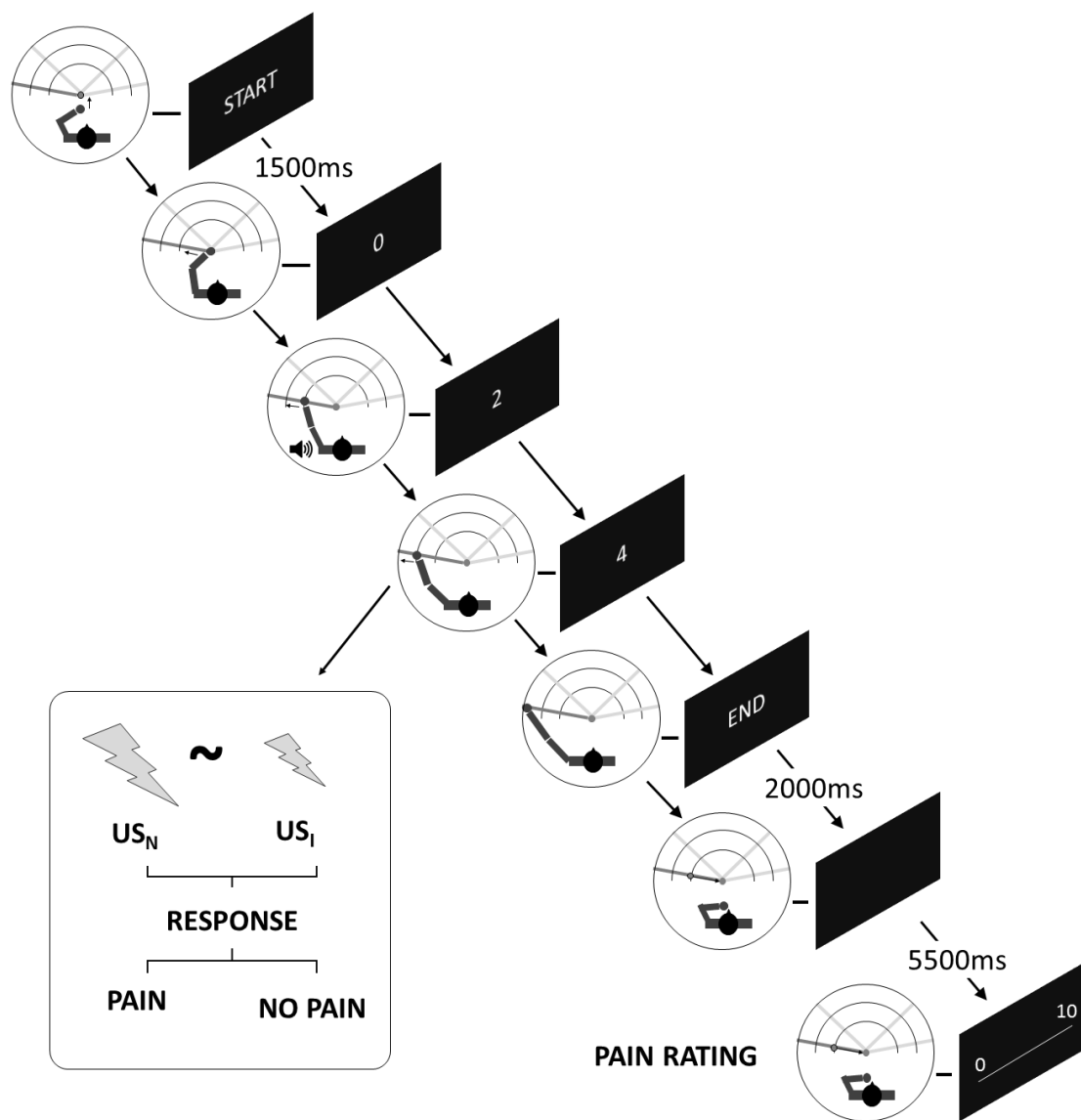
Fig. 2. Schematic representation of a trial flow. The artificial boundaries dividing the movement trajectory into segments are illustrated by the half circles. Eyeblick startle probes were presented when the first boundary was crossed, while the electrocutaneous stimuli were presented upon crossing of the second boundary.

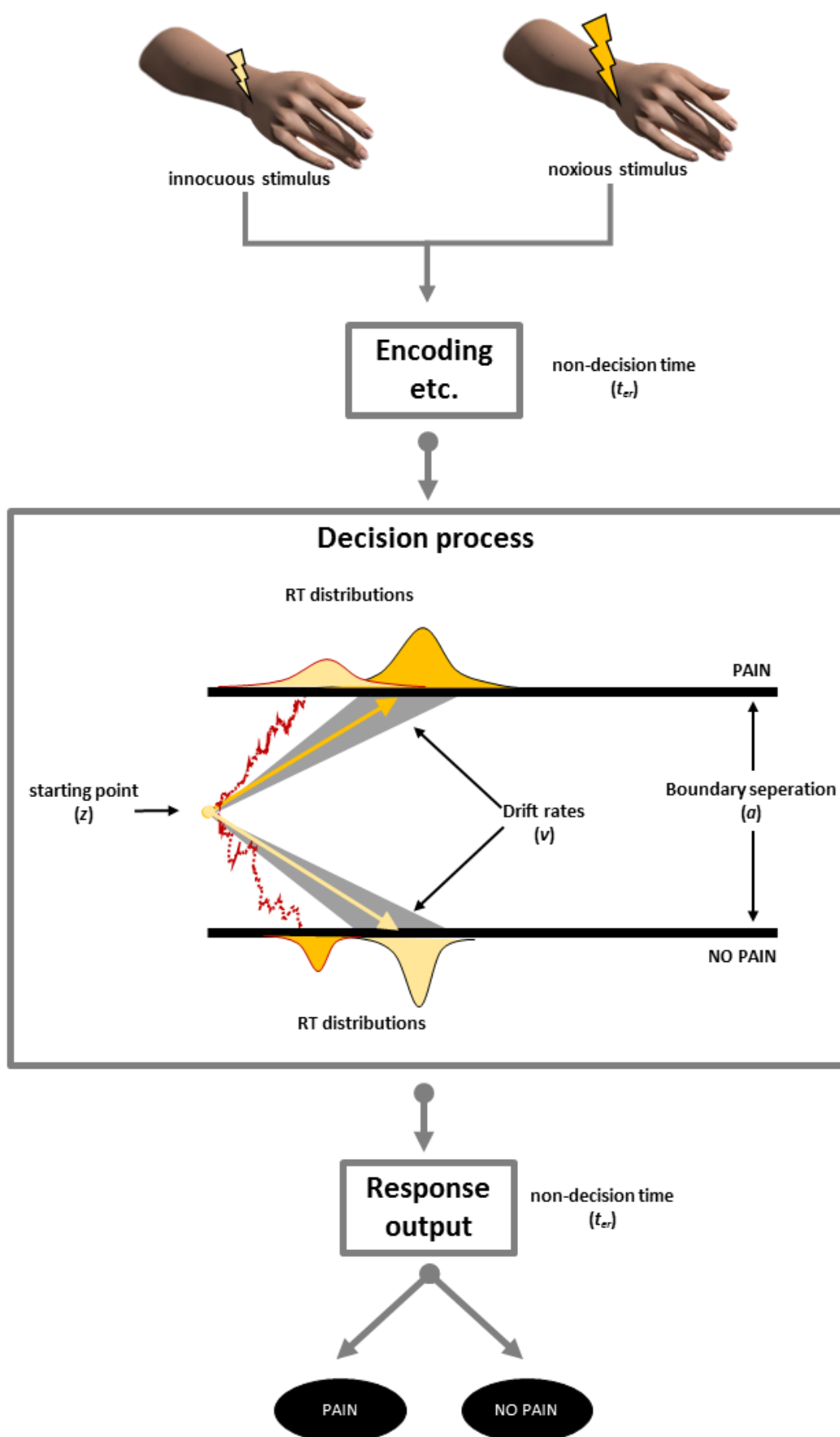
Fig. 3. (A) Mean pain ratings for the noxious (US_N) and innocuous US (US_I) categorized as pain or no pain in the predictable and unpredictable condition. (B) Mean categorization accuracies (red bars). Overall, participants reached a decision accuracy of 94.01% (SD = 7.65%) for US_I and 87.18% (SD = 13.00%) for US_N . (C-E) Estimated drift diffusion parameters averaged across participants (red bars).

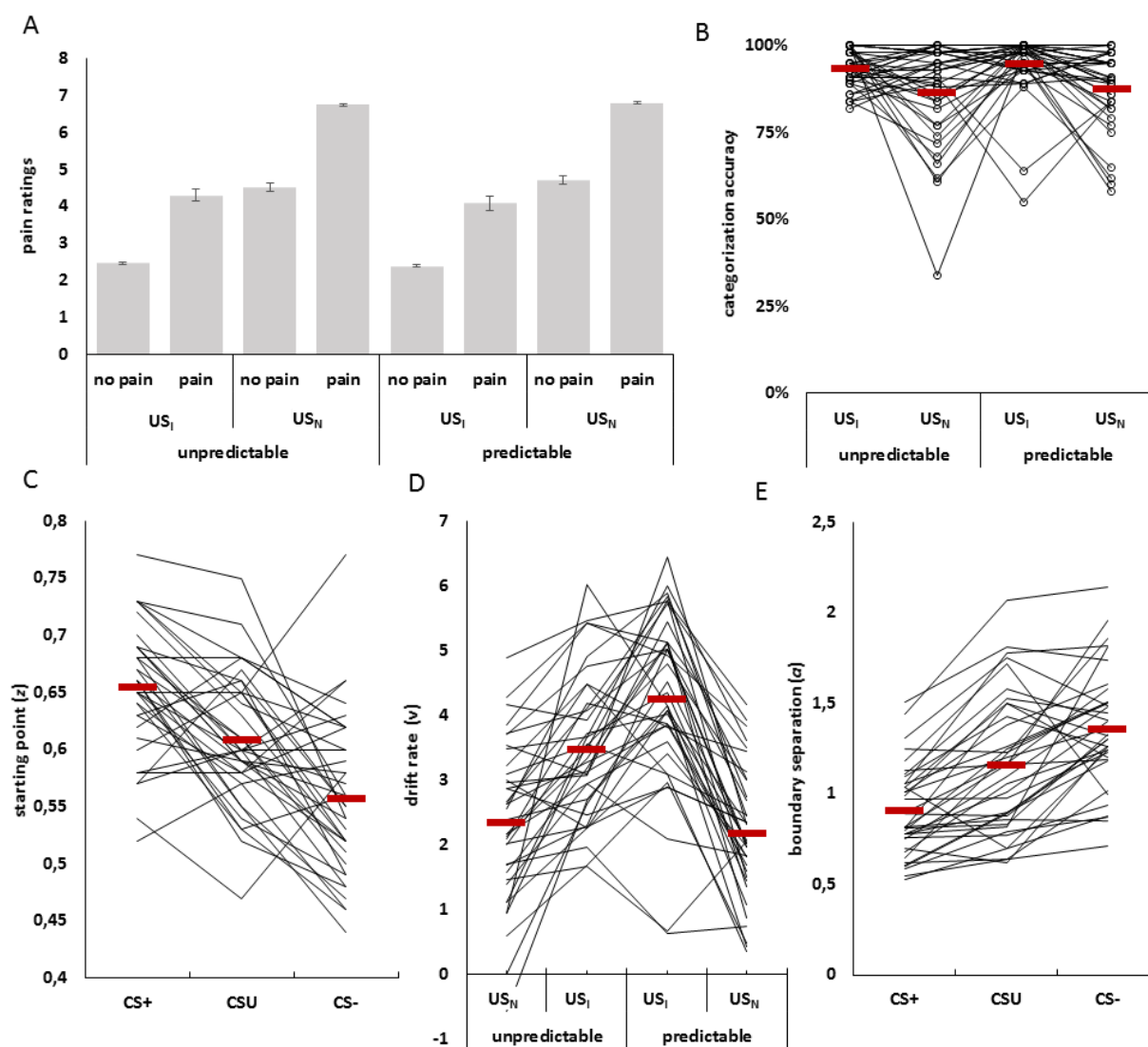
Fig. 4. Predicted pain rating of the mixed models for each of the estimated drift diffusion parameters (black lines). Dots represent averaged pain ratings per subject and stimulus (light circles = US_I ; dark circles = US_N).

Table legend

Average self-report ratings and startle amplitudes for the different CSs. Different superscripts denote differences at $p < .05$ corrected for multiple testing by a factor 3.







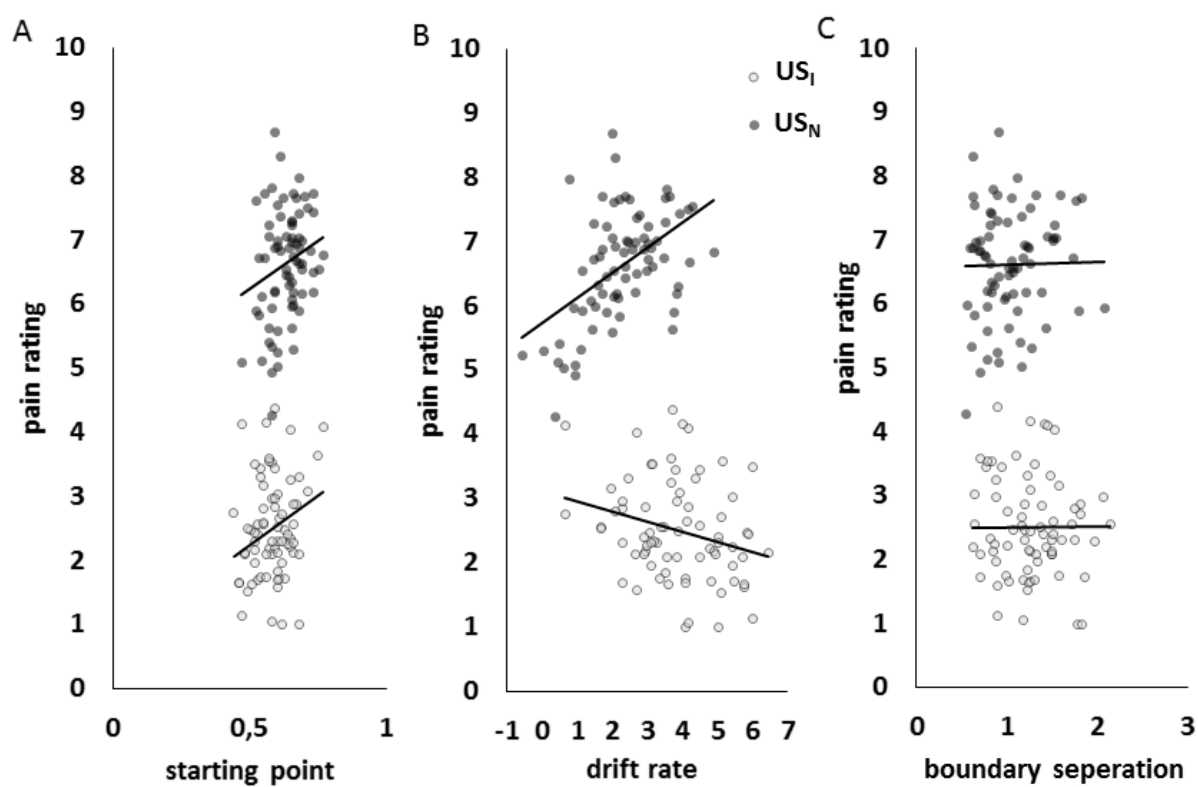


Table 1. Mean self-reports and startle amplitudes with standard deviations.

	Predictable		Unpredictable
	CS+	CS-	CS _u
Self-reported			
Tension (0-100)	56.51 (22.43) ^a	33.01 (22.27) ^b	47.07 (20.45) ^c
Fear (0-100)	51.30 (22.10) ^a	28.23 (21.63) ^b	43.50 (20.24) ^c
Unpleasantness (0-100)	55.71 (23.75) ^a	29.59 (21.26) ^b	43.67 (19.37) ^c
US-expectancy (0-100)	74.81 (21.09) ^a	38.45 (29.71) ^b	54.51 (19.02) ^c
Startle amplitudes	50.11 (3.25) ^a	48.63 (2.97) ^a	50.56 (2.25) ^a