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Sensitivity to Pain Expectations: A Bayesian Model of Individual Differences

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Word count (Excl. Abstract, Supplementary Material, Appendix & References): 8,944

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20 **Abstract**

21 The thoughts and feelings people have about pain (referred to as ‘pain expectations’) are known to
22 alter the perception of pain. However little is known about the cognitive processes that underpin pain
23 expectations, or what drives the differing effect that pain expectations have between individuals. This
24 paper details the testing of a model of pain perception which formalises the response to pain in terms of a
25 Bayesian prior-to-posterior updating process. Using data acquired from a short and deception-free
26 predictive cue task, it was found that this Bayesian model predicted ratings of pain better than other,
27 simpler models. At the group level, the results confirmed two core predictions of predictive coding; that
28 expectation alters perception and that increased uncertainty in the expectation reduces its impact on
29 perception. The addition to the model of parameters relating to trait differences in pain expectation,
30 improved its fit, suggesting that such traits play a significant role in perception beyond those expectations
31 triggered by the pain cue. When model parameters were allowed to vary by participant, the model’s fit
32 improved further. This final model produced a characterisation of each individual's sensitivity to pain
33 expectations. This model is relevant for the understanding of the cognitive basis of pain expectations and
34 could potentially act as a useful tool for guiding patient stratification and clinical experimentation.

35
36 Key words: Pain; Expectation; Uncertainty; Bayes; Perception; Placebo effect

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40 **1. Introduction**

41 The experience of pain, like all other sensory experience, is a result not only of the objective reality, such as
42 the degree of tissue damage, but also of the sufferer's beliefs about pain. Conscious and unconscious
43 thoughts and beliefs that people have about imminent pain are referred to as 'pain expectations'
44 (Schrooten, Vlaeyen, & Morley, 2012). The effect of pain expectations on pain experience is evident in both
45 laboratory and clinical experiments (e.g. Atlas & Wager, 2012; Bingel et al., 2011; Colloca, & Benedetti,
46 2006; Peerdeman et al., 2016; Tracey, 2010). In addition, neural correlates of the effect of expectation on
47 pain perception have been established (Brown, et al 2008a; Ploghaus et al., 1999; Seymour et al., 2004;
48 Tracey, 2010; Wager et al., 2004; Watson et al., 2009). Despite these advances there remains a significant
49 gap in our knowledge regarding the specific cognitive processes that underpin pain expectations.

50 Predictive coding provides the dominant theoretical framework for understanding the effects of
51 expectation on perception (Clark, 2013, Friston, 2003), including pain perception (Buchel, Geuter, Sprenger,
52 & Eippert, 2014; Tabor, Thacker, Moseley, & Körding, 2017; Van den Bergh, Witthöft, Petersen, & Brown,
53 2017). Predictive coding stipulates that perception is biased towards the expected level of pain, and that
54 this bias will be stronger when the expectation is more certain, since expectation uncertainty causes the
55 suppression of top-down, prior-driven signals, leading to greater importance being placed on the bottom-
56 up sensory input. A number of studies confirm the specific predictions of this theory for pain perception,
57 beyond the established biasing effect that pain expectations exert on pain experience. For example the
58 effect of pain expectations is enhanced when expectations are more precise (Brown, Seymour, Boyle, El-
59 Deredy, & Jones, 2008b; Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010). Likewise formal Bayesian
60 models provide a good fit to pain reports in placebo analgesia studies (Anchisi, Zanon, Plaghki, Kirsch, &
61 Claggett, 2015; Jung, Lee, Wallraven, & Chae, 2017) and to neural data from the anterior insula (Geuter,
62 Boll, Eippert, & Büchel, 2017).

63 Although predictive coding guides much of the research on the effect of expectations on perception,
64 some findings appear to contradict its prediction concerning the impact of the precision of the expected
65 pain. Watkinson et al., (2013) delivered two different distributions of pain stimuli, a unimodal and a

66 bimodal distribution. The two distributions had the same mean pain level, but the bimodal distribution had
67 a larger variance. According to predictive coding theories the mean expected level of pain should be the
68 same in the two conditions, but the influence of this expectation on pain experience should be lower in the
69 bimodal condition, as the larger variance of the bimodal distribution should cause greater expectation
70 uncertainty. In direct contradiction with predictive coding, and in support of the alternative, Range
71 Frequency Theory (Parducci., 1963), Watkinson et al., found that the expected mean level of pain had a
72 stronger influence on the rating of three target stimulations in the bimodal condition, despite the greater
73 uncertainty generated by the larger stimulation variance. Likewise, Yoshida et al., (2013) altered
74 participant's expectations relating to upcoming pain stimulation by presenting fictitious pain ratings of the
75 stimulus prior to their delivery. The mean and variance of the distribution of these ratings were
76 manipulated. They found that increasing pain uncertainty contributed independently to increased pain
77 experience, in contradiction with predictive coding. In addition, it is not clear from Yoshida et al. data
78 whether uncertainty significantly modulated the bias induced by the mean of the fictitious pain ratings, as
79 it should do according to the predictive coding framework. These findings suggest that further work is
80 needed before predictive coding is accepted as a viable framework for understanding pain perception.

81 Over and above the conflicting findings around the impact of expectation uncertainty, we also know
82 very little about how specific processes that underlie pain expectations are integrated. Unpacking the
83 construct of pain expectations to its underlying information processing mechanisms requires a statistical
84 model of the pain perception process to be formulated which accommodates parameters that describe
85 different facets of pain expectations. Furthermore, in order for such a model to be useful in understanding
86 an individual's response to both pain and placebo analgesia, it needs to be capable of predicting the effect
87 of pain expectations not just at a group level, but also at an individual level, and not only qualitatively, but
88 also quantitatively. For example such a model would need to be able to identify individuals that experience
89 high levels of pain because they have a trait-like bias to expect high levels of pain (i.e. always expecting high
90 pain, independent of context), and to distinguish such individuals from those who experience high pain
91 because they are highly pessimistic in assessing the information they are given about a treatment, or

92 because they are over-confident in their mildly-pessimistic expectations, so that they rely less on their
93 sensory data. That level of understanding is necessary to allow an individual's response to treatment to be
94 predicted, thus providing the basis for a tool that can support clinical decision making.

95 This paper details the construction and testing of a mathematical model of the impact of pain
96 expectations on pain perception using experimental data garnered from a novel predictive cue task. The
97 purpose of this model construction was threefold. Firstly, we wished to assess the effect of expectation
98 uncertainty on pain perception in light of the conflicting past results mentioned above. Our second
99 objective was to identify, using the experimental data, a number of putative cognitive processes that give
100 rise to the umbrella term 'pain expectations'. Finally, leading on from the second objective, we wished to
101 assess whether a model could be constructed that would enable individuals to be distinguished based on
102 the aforementioned cognitive processes.

103 We collected two sets of experimental data via two separate experiments using independent samples. A
104 series of increasingly complex statistical models were constructed and their performance was compared
105 using the data from the first experiment. The simplest model (Model 1), where the pain participants
106 experienced was influenced only by the actual, delivered pain, served as a baseline to compare to five other
107 models, which successively included additional facets of pain expectations (Table 1). The multi-modal
108 model (Model 2) represented pain expectations with a multi-modal distribution, which peaked around each
109 of the possible pain levels that participants could expect based on the cues they were given. In the 'Mean-
110 only model' (Model 3) pain expectations were assumed to correspond to the mean of the expected pain
111 (i.e. the average of the possible pain levels indicated by the cue). The 'Mean-and-variance model' (Model 4)
112 was inspired by predictive coding, and took into consideration the variance of expected pain, a function of
113 the discrepancy between the possible pain levels indicated by the cue. Like Model 3, Model 4 also allowed
114 pain experience to be affected by the mean of the expected pain, but here the impact of mean expected
115 pain was modulated by its uncertainty. Finally the 'Full model' (Model 5) additionally included the effect of
116 cue-independent pain expectations in addition to the cue-dependent expectations used in Models 2, 3 and
117 4. In this formulation, cue-dependent pain expectations relate to those triggered on each trial by the cue,

118 while cue-independent expectations capture more stable, trait-like differences in the propensity to believe
119 that pain will be greater or weaker, independent of the effect of specific local cues. Thus, this model is
120 organised into tiers, such that stable priors contribute to the shaping of more temporary priors triggered by
121 the information provided by the cue. Finally, to satisfy the objective of creating a model that can
122 characterise pain expectations at the individual level, we compared the winning group-level model to an
123 individual-level variant that included individual-level random effects (Model 6). We considered the winning
124 model to be able to usefully characterise pain expectations at an individual level if the ‘individual-level’
125 variant of the model was significantly better at predicting pain perception than its equivalent group level
126 variant. The second experimental dataset was used for the purposes of conceptual replication; enabling
127 validation of the findings from the first dataset, thus providing evidence that the winning model could
128 predict outcomes in a dataset other than the one from which it was constructed (cf. Maloney & Zhang
129 2010).

130 We hypothesised that the model comparison will provide support for the predictive coding framework.
131 More specifically we predicted, based on neural evidence that the mean of probabilistic cues is computed
132 and utilised in decision-making (Schultz, O’Neill, Tobler, & Kobayashi, 2011), that Model 3 will provide a
133 better fit to the data than Model 2. We also predicted that Model 4 will provide a better fit to the data than
134 Model 3, thus showing that expectation uncertainty significantly affects pain perception; and that the value
135 of model parameter describing the effect of expectation uncertainty will show that increased uncertainty
136 reduces the influence of pain expectations. Based on the vast clinical literature on individual differences in
137 pain catastrophizing (Sullivan, Bishop, & Pivik, 1995) we hypothesised that Model 5 will provide a better fit
138 for the data than Model 4, suggesting that both cue-dependent and cue-independent expectations have
139 separate influences on pain perception. Finally, we hypothesised that when individual-level random effects
140 are added to the winning model this will significantly improve the fit of the model to the data, suggesting
141 that the model is able to characterise sensitivity to pain expectations at an individual level.

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143

144 **2. Method**

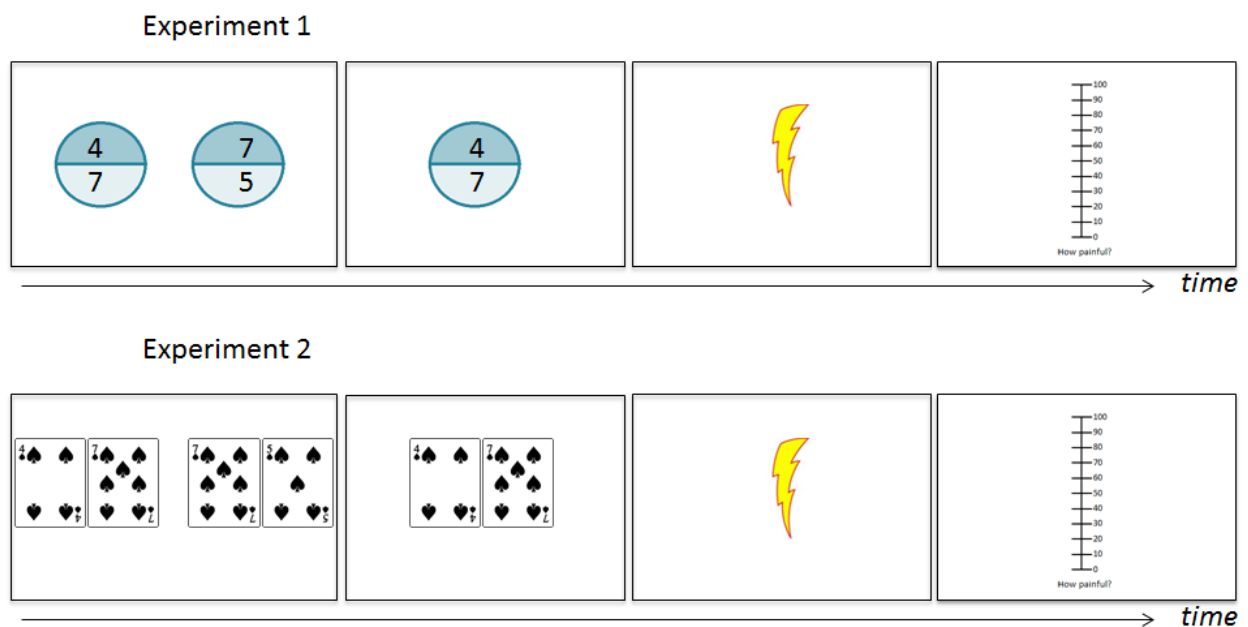
145 **2.1 General experimental design**

146 Two experiments were conducted on independent samples. Experiment 2 was conducted for validation,
147 with task delivery modifications introduced to enhance the translational impact of the approach. During
148 each experiment participants performed a ‘pain rating’ task (Figure 1.). In each trial of the task,
149 participants’ expectations regarding the upcoming stimulation were manipulated. This manipulation was
150 achieved by offering the participants a choice between two ‘cues’ expressing different probability
151 distributions for the intensity of the upcoming stimulation in terms of the possible intensities and
152 corresponding probabilities. After selecting one of the cues the participant then experienced a pain
153 stimulation level generated in accordance with the probabilities represented by the selected cue. Finally,
154 the participant was required to rate the intensity of the stimulation they received. This choice mechanism
155 was used (in contrast to just presenting participants with one cue) to ensure that the participants both
156 attended to, and understood, the pain probability cues they were presented with. The choice mechanism
157 also acted to give the participants a sense of control over the upcoming pain, so as to minimise the possible
158 influence of learned helplessness on their pain experience (Bhat et al., 2010). The trials were designed in
159 such a way that one cue (herein referred to as the ‘target’) was always preferable to the other (herein
160 referred to as the ‘lure’) in terms of expected pain intensity. Trials where the participants chose the lure (or
161 failed to make a choice at all) were discarded from the data analysis as in such instances it was not certain
162 that the participants had understood the cues. The targets were created in accordance with a design that
163 allowed a systematic manipulation of the relevant aspects of pain expectation.

164 The task utilised here is novel in the context of pain research. However, it has been used extensively to
165 examine how people value financial outcomes (Talmi, Atkinson, & El-Deredy, 2013) as well as taste and
166 pain outcomes (Hird et al., 2017). It differs from placebo paradigms because the manipulated quantity is
167 the individual’s expectation about the impending pain, rather than about the efficacy of treatment. One
168 particular feature of this task (in contrast with placebo and other cue-based paradigms) is the avoidance of
169 deception. In placebo paradigms participants are told that an ineffective intervention (e.g. an inert cream)

170 is in fact a proven treatment (e.g. an active analgesic). In current cue-based paradigms (e.g. Atlas et al.,
171 2010), cues intentionally mislead participants, for example informing them that an impending pain stimulus
172 will be high intensity, when it may in fact be of moderate intensity. We avoided deception firstly because
173 the integrity of data resulting from deception paradigms is reliant on the participant remaining naïve to the
174 deception throughout the experiment, and secondly because deception is problematic as far as translation
175 into clinical settings is concerned. Files needed to run the experimental paradigms, the analysis code and
176 the complete datasets are available to download from BioRxiv.

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178

179 **Figure 1. Schematic of one experimental trial in experiments 1 (top) and 2 (bottom).** Each trial began with
180 a cue selection phase (left panel) where the participant had to choose between two cues. Participants who
181 understand these cues should choose the left, target cue to minimise the chances of receiving strong pain.
182 Once a cue was selected it appeared on its own for 2s (second panel). This selected cue was assumed to
183 influence participants' pain expectations. Here the selected cue gives the participant 50% chance of
184 receiving pain level '4' and 50% of receiving pain level '7'. With this cue selected the expected pain level for
185 a participant who is not particularly anxious or overly optimistic is 5.5. Participants then received a painful
186 electric stimulation corresponding to one of the levels depicted on the selected cue, e.g. a '4' (third panel).

187 *Finally the participant rated their pain experience (fourth panel). In Experiment 1 the size of the portion on*
188 *which the number was displayed corresponded to the probability of receiving pain of that level. In*
189 *Experiment 2 all probabilities were fixed to 50%.*

190

191 **2.3 Experiment 1: Method**

192 *2.3.1 Experimental design*

193 The top panel of Figure 1 shows an example of a trial from Experiment 1. In this example the ‘target’ cue
194 presented a 50% chance of receiving level 4 pain and 50% chance of receiving level 7 pain. This target
195 therefore provided an expected pain intensity of 5.5, and is therefore preferable to the ‘lure’ cue, which
196 presents a 50% chance of receiving level 5 pain and 50% chance of receiving level 7 pain (expected intensity
197 = 6). The cues were designed to provide a balanced manipulation of the following variables across the
198 sequence of trials experienced by each individual: the expected value of the pain (the mean: 4.5, 5.5), the
199 number of different pain levels that could potentially be delivered (2, 4), the prediction error (the
200 difference between expected level of pain and intensity of the delivered stimulation: 0.5, 1.5) and the sign
201 of the prediction error (positive or negative). Using the trial depicted in Figure 1 as an example, if the target
202 cue was selected and the level 7 pain subsequently delivered, then the prediction error would be +1.5 (7 -
203 5.5). The positive sign of the prediction error indicates that the pain level that was experienced was higher
204 than the average pain level participants would expect on the basis of the cue they selected. In summary,
205 the experimental corresponded to a 2 (mean expected pain: 4.5, 5.5) x 2 (number of cue options: 2, 4) x 2
206 (direction of the prediction error: positive, negative) x 2 (the size of the prediction error: 0.5, 1.5) design.

207

208 *2.3.2 Participants*

209 Sixteen undergraduates from the Manchester University School of Psychological Sciences (14 female, Mean
210 age 19.6, $\sigma = 1.36$) participated in the study for course credit. Participants were excluded if they had a
211 history of psychiatric or neurological disorders. All participants achieved the criterion performance level of

212 85% correct responses (defined as choosing the target cue during the pain rating task). The study received
213 ethical approval from the North West 6 Research Ethics committee (Greater Manchester South).

214

215 *2.3.3 Materials*

216 Acute experimental pain was delivered to the participants using electric stimulation, which has been shown
217 to produce effects of expectations that are equivalent to those produced with the more typical laser
218 stimulation (Hird, Jones, Talmi, & El-Deredy, 2018). Compared to laser pain, which is used more often in the
219 laboratory, the electric stimulation method is safe to use repeatedly and easier to implement in clinical
220 settings. The electrical stimulations were delivered to the back of the right hand via a ring electrode built
221 in-house (Medical Physics, Salford Royal Hospital) attached to a Digitimer DS5 Isolated Bipolar Constant
222 Current Stimulator (www.digitimer.com). To ensure adequate conductance between the electrode and the
223 skin, the back of each participant's hand was prepared with Nuprep Skin Preparation Gel and Ten20
224 Conductive Paste prior to the electrode being attached. The experimental paradigm itself was delivered via
225 a laptop using Cogent2000 on a Matlab platform (www.Mathworks.com). The inputs to the DS5 machine
226 were sent from Matlab via the Spike2 software (www.ced.co.uk) and a 1401plus data acquisition interface
227 (www.ced.co.uk).

228 Cues consisted of charts which were 240 pixels in diameter and which used colours that were
229 equiluminant (thus making each chart equiluminant). These charts used combinations of the 5 pain levels
230 (3,4,5,6,7) and 6 different proportions (25%, 33%, 50%, 67%, 75%, 100%) to manipulate aspects of the pain
231 expected (Supplementary Table2.)

232

233 *2.3.4 Procedure*

234 Participants were given an information sheet prior to the study informing them of the justification for the
235 study and of the use of electrical stimulation. On arriving at the laboratory participants were first asked to
236 sign a consent form, and then to confirm that they had read the information sheet. The electrode was then

237 attached to the back of the participant's right hand. Once the electrode was attached the participants
238 undertook a pain calibration procedure. This procedure was necessary firstly to ensure that the participant
239 could tolerate the stimulations, and secondly to ensure that the stimulations were psychologically
240 equivalent across participants. Once the pain calibration procedure was complete participants were given
241 instructions relating to the pain rating task. Participants were then given 6 practice trials of the pain rating
242 task before undertaking the task proper.

243

244 *2.3.4.1 Pain calibration.*

245 During this procedure participants received a series of stimulations, starting from 0.2V, and incrementing
246 by 0.2V at each step. Participants rated each stimulation on a scale from 0 – 10 where a score of 0 reflected
247 not being able to feel the stimulation, 3 reflected a stimulation level that was on the threshold of being
248 painful, 7 related to a stimulation that was deemed 'painful but still tolerable' and 10 related to
249 'unbearable pain'. The scaling procedure was terminated once the participant reported the level of pain as
250 being equivalent to '7' on the scale. This calibration procedure was performed twice to allow for initial
251 habituation/sensitisation to the stimulation. The voltage levels rated as '3', '4', '5', '6', and '7' on the
252 second run of the calibration procedure were used as the different pain levels to be delivered during the
253 pain rating task. The average voltage used for each pain level are shown in Supplementary Table 1.

254

255 *2.3.4.2 Pain rating task.*

256 Each trial began with a 250ms fixation cross, before two cues, presented as two pie charts, appeared side-
257 by-side on the screen (+/- 160 pixels from the centre: Figure 1). Participants were required to choose
258 between these cues using the mouse. Numbers on the 'slices' of each pie chart indicated the level of
259 stimulation that the slice related to, while the size of the slice depicted the probability of the stimulation
260 level being delivered if the cue was selected. Participants had up to 8 seconds to make their selection. The
261 target cue was always clearly preferable to the lure in terms of expected pain value (see General Methods).
262 If the participant failed to make any selection within the 8s time limit then the lure cue was automatically

263 selected. The selected cue was then presented alone in the centre of the screen for 2 seconds, at which
264 point the cue disappeared and one of the pain levels depicted on the cue was delivered to the back of the
265 hand according to the probabilities depicted on the cue. Finally a visual-analogue scale (Hjermstad et al.,
266 2011) ranging from 0-100, appeared 500ms after the offset of the stimulation. Participants were required
267 to rate their experience of the stimulation on this scale using the mouse, with the trial only proceeding
268 once a rating had been given. Participants were told that even though the stimulation they would receive
269 would always be one of those predicted by the selected cue, they should rate the pain they actually felt.
270 The use of a 0-100 rating scale gave the participants sufficient scope to report trial-by-trial differences in
271 pain experience, while preventing them from simply reporting which intensity they thought had been
272 delivered (which would be a possibility if participants were asked to rate their experience using the same 0-
273 10 scale used during the pain calibration task). The starting position of the cursor (on the rating scale) was
274 randomised on a trial-by-trial basis, eliminating systematic biases of the expectations on the motor
275 response. After the rating was provided an inter-trial interval occurred of a length selected randomly from
276 1000, 1500, 2000, 2500 & 3000ms (average 2000ms).

277

278 *2.3.4.3 Experimental task.*

279 Participants undertook 5 blocks of trials, with 32 trials in each block, giving a total of 160 trials. Each block
280 consisted of a randomised presentation of 24 types of trials, depicted in Supplementary Table 2. In 16 of
281 these the target cue corresponded to one of the 16 experimental conditions according to the 2x2x2x2
282 experimental design described above. Four additional trial types were required to complete the design (see
283 Supplementary Table 2). Four further trials types, involving target cues which depicted the delivery of pain
284 levels 3, 4, 5 and 6 with 100% probability, were included for the purpose of a manipulation check. A self-
285 timed break was given every 20 trials.

286

287 **2.4 Experiment 2: Method**

288 The design of Experiment 2 was similar to that of Experiment 1. The following changes were made with the
289 potential clinical application of the paradigm in mind. Firstly, sets of playing cards were used as cues
290 instead of pie charts (Figure 1). This allowed the results from Experiment 1 to be (potentially) replicated
291 using cues that may be more readily understood by a clinical audience. Secondly only trial types involving 2
292 different intensities with equal (50%) probabilities were included in the design. This meant that only 3
293 aspects of pain expectation were manipulated within participants; the expected pain level (4.5, 5, 5.5), the
294 size of the prediction error (0.5, 1.5, 2), and the direction of the prediction error (positive or negative). This
295 change allowed a reduction to the number of trials appearing in the experiment, and therefore a reduction
296 in the length of the experiment. This was thought beneficial due to the limited time available in the clinic
297 for diagnostic procedures.

298

299 *2.4.1 Participants*

300 Thirty-two undergraduates from the Manchester University Psychology Department (26 female, Mean age
301 19.3, $\sigma = 1$) participated in the study for course credit. Participants were excluded if they had a history of
302 psychiatric or neurological disorders. The study received ethical approval from the North West 6 Research
303 Ethics committee (Greater Manchester South). Data from three participants was excluded because they did
304 not achieve the criterion performance level of 85%, leaving a sample of 29 (24 female, mean age 19.3, $\sigma =$
305 1).

306

307 *2.4.2 Materials and procedure*

308 The materials were the same as in Experiment 1, but instead of charts, the cues consisted of spade suit
309 playing cards. Each cue took the form of a pair of playing cards (100x130 pixels in size), with each card
310 corresponding to one slice of the charts used in Experiment 1. During the selection phase the two cards
311 from each pair of cards were presented 225 and 100 pixels from the centre of the screen, with one pair

312 being presented to the left of the screen and the other to the right. After selection, the two cards
313 comprising the selected cue were presented +/- 75 pixels from the centre of the screen.

314 Participants undertook 5 blocks of trials. Each block consisted of a randomised presentation of 16 types of
315 trials depicted in Supplementary Table 3. In 8 of these, the target cue corresponded to one of the 8
316 experimental conditions in a 2 (the expected pain level: 4.5, 5.5) x 2 (the size of the prediction error: 0.5,
317 1.5) x 2 (the direction of the prediction error: positive or negative) experimental design. In 4 trial types the
318 target cue corresponded to one of the 4 experimental conditions in a 2 (the size of the prediction error: 0.5,
319 1.5) by 2 (the direction of the prediction error: positive or negative) experimental design. We employed
320 these two designs together in order to compare their efficacy, and decide which design was best for future
321 experiments. Four additional trial types involving target cues which depicted the delivery of pain levels 3, 4,
322 5 and 6 with 100% probability were again included for the purpose of a manipulation check. In total,
323 therefore, each participant undertook 80 trials, with self-timed breaks given every 20 trials. The average
324 voltage used for each pain level during the experiment are shown in Supplementary Table 1.

325

326 **2.5 Statistical analysis**

327 *2.5.1 Modelling*

328 The predictive coding framework suggests that our perceptual systems are organised in a hierarchical
329 manner. Within this framework perceptual systems at a high level in the hierarchy hold prior distributions
330 relating to sensory input which are shaped by past experience. Perceptual expectations at any specific point
331 in time arise from these prior distributions. For example, during pain perception, the prior distributions
332 (priors) held at high levels of the hierarchy, are compared to incoming pain at lower levels. Discrepancies
333 between the priors and sensory input are then projected back to the higher level, causing the prior to be
334 updated into a posterior distribution (from which the resulting pain experience arises) while also altering
335 the basis on which subsequent priors will be calculated (Buchel et al., 2014). The models presented in this
336 paper are influenced by this framework, formalising response to pain in terms of a Bayesian prior-to-

337 posterior updating process. Apart from the baseline model, we consider 5 Bayesian models, which are all
338 based on a multiplicative decomposition of the joint probability that conforms to the Bayes theorem, under
339 the stipulated assumptions. These 5 models can be considered Bayesian because they allow a prior
340 distribution representing pain expectation to be updated, on the basis of sensory information, into a
341 posterior distribution representing the final perceptual experience. The models are Bayesian also in that
342 they regard model parameters as random variables. From a statistical standpoint the full version of these
343 Bayesian models is ‘hierarchical’ in that it involves a multilevel Bayesian structure consisting of two levels
344 (tiers) of the model specification:

- 345 1. a bottom level where distribution is specified conditional on unknown model parameters
- 346 2. a top level which specifies a distribution of the parameters which (in the final model) are allowed to
347 vary from one individual to the next according to an exchangeable population distribution.

348 For participant i during trial j we represent the pain stimulation that was delivered as X_{ij} and the pain they
349 reported as R_{ij} , both expressed on a 0-100 scale. The ratings were linearly transformed ($R_{ij} \rightarrow R'_{ij} = a_i +$
350 $b_i \times R_{ij}$) using the pain responses on the 100% probability trials to standardize the responses across
351 participants so as to avoid issues of differential scale use. Thus a_i and b_i were selected to minimize the
352 squared error between participants’ ratings and the delivered intensity. Before the pain stimulation was
353 delivered, participant i at the j th trial also saw a cue. Let the cue consist of information Z_{ij} , involving the
354 possible magnitudes ($v_{1ij} \dots v_{m_{ij}ij}$) of the incoming pain stimulus, also expressed on a 0-100 scale, and
355 their corresponding probabilities of occurrence, ($w_{1ij} \dots w_{m_{ij}ij}$). Thus conditional on Z_{ij} , the intensity of
356 the incoming pain stimulus has mean q_{ij} and standard deviation sd_{ij} respectively given by

$$357 \quad q_{ij} = \sum_{k=1}^{m_{ij}} w_{kij} v_{kij} \qquad sd_{ij} = \sqrt{\left(\sum_{k=1}^{m_{ij}} w_{kij} (v_{kij} - q_{ij})^2 \right)}$$

358 On the j th trial, an individual i exposed to cue Z_{ij} represents the predicted intensity of the upcoming
359 pain as a probability distribution $P(R_{ij} | Z_{ij})$. In the terminology of predictive coding, this is the ‘prior
360 distribution’ of the intensity of the upcoming pain. We formulate $P(R_{ij} | Z_{ij})$ as a product of two normal

361 distributions, one incorporating cue-independent information and the other incorporating the cue
362 information (see appendix for derivation):

363 1) $P(R_{ij} | Z_{ij}) \propto \text{Normal}(q_{ij}, \rho + \eta \times sd_{ij}) \times \text{Normal}(\mu, v)$

364 where the symbol \propto stands for “proportional to” and $\text{Normal}(x, y)$ stands for the normal distribution
365 with mean x and standard deviation y , occasionally truncated to ensure that random variables satisfy their
366 range constraints, whenever appropriate.

367 The cue-independent $\text{Normal}(\mu, v)$ represents a stable, trait-like bias to expect pain of a certain
368 intensity independently of the cue. Higher values of parameter μ indicate higher values for the mean of the
369 cue-independent prior (and thus reflect the expectation of higher levels of pain, independent of any cue
370 information). Higher values of parameter v (the standard deviation of the cue-independent prior) reflect
371 greater uncertainty (and therefore lesser influence) of this cue-independent prior. Participants with high μ
372 and low v can be thought of as pessimistic about pain. The cue-dependent $\text{Normal}(q_{ij}, \rho + \eta \times sd_{ij})$
373 represents the effect of the cue information Z_{ij} on the predicted (pre-stimulus) rating. The parameter ρ
374 controls the precision of this prediction. Parameter η modulates this precision according to the cue’s
375 variance, such that increasing values of η indicate a greater detrimental effect of variance within the cue on
376 the precision of the prediction. The influence of the cue thus increases with lower values of ρ and η .
377 Together, these parameters determine the extent to which the cue information modulates the prior
378 distribution, and thus the subsequent experience of pain.

379 The stimulation causes the prior distribution to be updated into a posterior. The posterior distribution
380 $P(R_{ij} | X_{ij}, Z_{ij})$ governs the pain intensity that the individual experiences and rates. Following from Bayes’
381 theorem, the posterior is given, up to a proportionality constant, by the product of the likelihood of the
382 stimulation and the prior:

383 $P(R_{ij} | X_{ij}, Z_{ij}) \propto P(X_{ij} | R_{ij}, Z_{ij}) \times P(R_{ij} | Z_{ij})$

384 In the appendix we justify the following:

385 2) $P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times P(R_{ij} | Z_{ij})$

386 In this term, each predicted value of R_{ij} is compared with the external sensory information, associating
387 each such value with a measure of 'surprise', which our model takes to increase with an increasing distance
388 between R_{ij} and the actual intensity of the stimulation, X_{ij} . The value of β determines the extent that the
389 perceptual mechanism will tolerate a given disparity between the predicted experience and the actual
390 sensation, with smaller values of β implying greater sharpness of the likelihood function around X_{ij} and
391 hence a reduced tolerance. Plugging Equation 1 into Equation 2 we get the full model:

392 3) $P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times \text{Normal}(q_{ij}, \rho + \eta \times sd_{ij}) \times \text{Normal}(\mu, v)$

393 Here the prior is combined with the surprise in accord with the Bayesian formalisation of the
394 integration of multiple sources of evidence. The multimodal prior model (Model specification section
395 below) elaborates the second term of Equation 3 into a mixture of normals

396

397 2.5.2 Model specification

398 Data from each experiment were analysed separately with the following models:

399

400 1. *Baseline model*: This model assumes that pain experience depends solely on the pain stimulation. No
401 effect is attributed to pain expectations, whether arising from the cue, or from cue-independent effects of
402 the prior.

403 $P(R_{ij} | X_{ij}, Z_{ij}) = P(R_{ij} | X_{ij}) = \text{Normal}(X_{ij}, \beta)$

404 2. *Multimodal prior model*: In this model pain experience depends not only on the pain stimulation, but also
405 on the information in the cue, where that information is represented by a multi-modal weighted mixture of
406 normals. The spread of each normal component of this mixture is modulated by the parameter ρ . The
407 normals are centered at each possible magnitude ($v_{1ij} \dots v_{m_{ij}ij}$) of the incoming pain stimulus and are
408 weighted by their corresponding probabilities of occurrence, ($w_{1ij} \dots w_{m_{ij}ij}$).

409
$$P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times \left[\sum_{k=1}^{m_{ij}} w_{kij} \times \text{Normal}(v_{ij}, \rho) \right]$$

410

411 *3. Mean-only model:* As with Model 2, in this model pain experience again depends not only on the pain
412 stimulation, but also on the information in the cue. Unlike Model 2 however, the cue information is
413 represented by the mean of the cue, q_{ij} , modulated by the parameter ρ .

414
$$P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times \text{Normal}(q_{ij}, \rho)$$

415 *4. Mean and Variance model:* Pain experience depends not only on the pain stimulation, but also on the
416 mean and variance of the cue. These influence the uncertainty of the prior distribution of R_{ij} such that cues
417 with higher sd_{ij} (modulated by η) influence the posterior less than precise cues.

418
$$P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times \text{Normal}(q_{ij}, \rho + \eta \times sd_{ij})$$

419 *5. Full model:* In this model pain experience is determined jointly by the pain stimulation and two tiers of
420 expectations: stable cue-independent effects akin to optimism/pessimism trait and effects informed by the
421 cue. Cue-independent effects are represented by a probability distribution with mean μ and variance v ,
422 which is integrated with the information provided by the cue to form the final prior distribution.

423
$$P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times \text{Normal}(q_{ij}, \rho + \eta \times sd_{ij}) \times \text{Normal}(\mu, v)$$

424 *6. Hierarchical model:* In this model pain experience is also determined jointly by the pain stimulation and
425 two tiers of expectations (as in Model 5), however in this model the parameters are now allowed to vary by
426 participant.

427
$$P(R_{ij} | X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta_i) \times \text{Normal}(q_{ij}, \rho_i + \eta_i \times sd_{ij}) \times \text{Normal}(\mu_i, v_i)$$

428

429

430 *2.5.3 Inference*

431 All the models in our analysis included a specification of the likelihood of the modeled observed quantities
432 X and R , given the model unknown parameters and the non-modeled observables, Z , plus a specification of
433 a (possibly uniform) prior distribution for the unknown parameters. Data from each experiment were
434 analysed separately. After each fitting, the goodness of fit of the model to the data was assessed via the
435 Deviance Information Criterion (DIC, Spiegelhalter et al., 2002) which penalises models for increasing
436 complexity. This criterion is sensitive to non-normalities of the posterior distributions of the parameter. An
437 exploration of these posteriors did not reveal departures from normality that might raise concern. At any
438 rate, in order to protect from any anomalous behaviour of DIC, we ranked the models also in terms of a
439 cross-validated measure of performance, specifically, leave-one-subject-out (LOSO) cross-validation (Xu &
440 Huang., 2012). In LOSO, the data for each experiment is partitioned by participant. For each partition the
441 models are fit with the remaining data from the same experiment and a log likelihood of the hold out data
442 is calculated. The DIC-based ranking and the cross-validated ranking were identical.

443 Using data from Experiment 1, we first compared fixed-parameter models 1-5 where all participants
444 shared the same values for the parameters. In these comparisons the baseline model (Model 1) serves as
445 the null hypothesis, as it assumes that the cue exerts no effect on pain experience, namely, no effect on the
446 prior and thus no effect of expectations of any kind. The comparison between the mean-only model (Model
447 3) and the multimodal model (Model 2) serves to assess the relevance of the expected value of the cue.
448 Following these comparisons, the same data were analysed with an elaboration of the winning fixed-
449 parameters model, now allowing the parameters β , ρ , η , μ , and ν , and to vary across individuals (the
450 ‘Hierarchical’, Model 6). We took the values of these parameters in individual i (respectively denoted by β_i ,
451 ρ_i , η_i , μ_i , and ν_i), to be independently drawn from corresponding population-level normal distributions, with
452 hyperparameters independently drawn from flat hyperprior distributions, resulting in a multilevel model.
453 This model allows us to describe the variability of the individual-specific posterior estimates for parameters,
454 and therefore to infer how the parameters vary across the population. Finally, we fitted these models to

455 data from Experiment 2, to provide validation that the findings from the first dataset would generalise to
456 an independent dataset.

457 As regards parameter estimation, the models, when combined with data, gives rise to a Bayesian
458 posterior distribution for the unknown model parameters. We sampled this posterior by using the
459 Hamiltonian dynamics Markov chain Monte Carlo (HDMCMC) techniques (Metropolis, Rosenbluth,
460 Rosenbluth, Teller, & Teller, 1953; Neal, 2012) incorporated in the program Stan (Stan Development Team,
461 2014a, 2014b). Any summary of the marginal posterior for any parameters of inferential interest can be
462 reconstructed on the basis of the sampled value for that parameter, generated by the Markov chain after a
463 suitable number of "warm-up" iterations. Initial values for the Markov chains were obtained via variational
464 inference techniques (Wainwright, & Jordan, 2008) based on a parametric approximation of the model
465 posterior.

466

467

468 **3. Results**

469 The average performance during the cue selection task (i.e. proportion of targets selected) was 96% in
470 Experiment 1 and 97% in Experiment 2, suggesting that participants understood the task well. In both
471 experiments the mean ratings given during the trials where the cue provided 100% chance of a particular
472 stimulation intensity increased linearly as a function of increased stimulation levels, confirming that
473 participants were able to distinguish between the stimulation levels (Supplementary Table 4).

474 Table 1 summarizes the DIC and LOSO log likelihood values for the fixed-parameter models. Lower DIC
475 values indicate higher likelihood of the data being generated by the model and thus better fit. Higher LOSO
476 values (lower in absolute value) also indicate a better fit. A difference greater than 10 between the DICs for
477 two models is considered strong evidence against the model with the higher score. For Experiment 1,
478 Model 1 fitted the data less well than the other models, which have all assumed that the cue has some
479 effect on the rating. The 'Mean-only model' (Model 3) fitted the data better than the 'Multimodal model'
480 (Model 2) justifying the use of the mean of the cue as a useful property of the cue information. The best-

481 fitting fixed-parameter model was the 'Full model' (Model 5). This finding supports the hypothesis that
 482 both cue-dependent and cue-independent biases influence pain perception. When the same models were
 483 tested using the data from Experiment 2, the results of the model comparisons were the same (Table1).

484

		Model Name	DIC		LOSO Log Likelihood	
			Exp 1	Exp 2	Exp 1	Exp 2
Fixed	1	Baseline model	17007	17304	-8507	-8657
	2	Multi-modal Model	16380	16793	-8193	-8403
	3	Mean-only model	16178	16179	-8094	-8096
	4	Mean & variance model	16138	16107	-8073	-8063
	5	Full model	15937	15714	-7981	-7875
Variable	6	Hierarchical model	15588	15047	-7871	-7648

485 **Table 1: DIC and LOSO log likelihood values for fixed and variable-parameter models.**

486

Parameter	Experiment 1		Experiment 2	
	Mean	Standard Error	Mean	Standard Error
β	8.97	0.18	9.45	0.21
ρ	6.331	0.37	8.20	0.45
η	0.12	0.020	0.09	0.024
μ	46.05	0.57	45.61	0.42
ν	12.04	0.49	10.67	0.28

487 **Table 2: Estimates of the model parameters arising from the full model.** *Parameter values from the 'Full*
 488 *model' (Model 5), where the parameters are assumed to be identical across the participants. The values in*
 489 *the table represent the mean and standard error (the standard deviation of the marginal posterior*
 490 *distribution) of each estimated parameter, respectively. The corresponding credible interval, defined for*
 491 *each parameter by the mean plus/minus 1.96 times the standard deviation, can be interpreted to contain*
 492 *the true value of the parameter with probability 0.95. The model parameters can be described as follows.*

493 *β : This parameter controls how likely is a value of R_{ij} conditional on X_{ij} , as a function of the distance*
494 *between the values of R_{ij} and X_{ij} .*

495 *ρ : The increase in the standard deviation of prior distribution of R_{ij} due to a unit increase in the mean of*
496 *the cue q_{ij} . This parameter controls how likely is a value of R_{ij} which is distant from q_{ij} , compared to a*
497 *value of R_{ij} which is close to q_{ij} .*

498 *η : The increase in the standard deviation of the prior distribution of R_{ij} due to a unit increase in the*
499 *standard deviation of the cue (sd_{ij}). This parameter captures an effect of the disparity (variance) in*
500 *possible pain levels described in the cue on the precision of the prior.*

501 *μ : The mean of the distribution of the predicted pain intensity prior to seeing the cue.*

502 *v : The standard deviation of the distribution of predicted pain intensity prior to seeing the cue.*

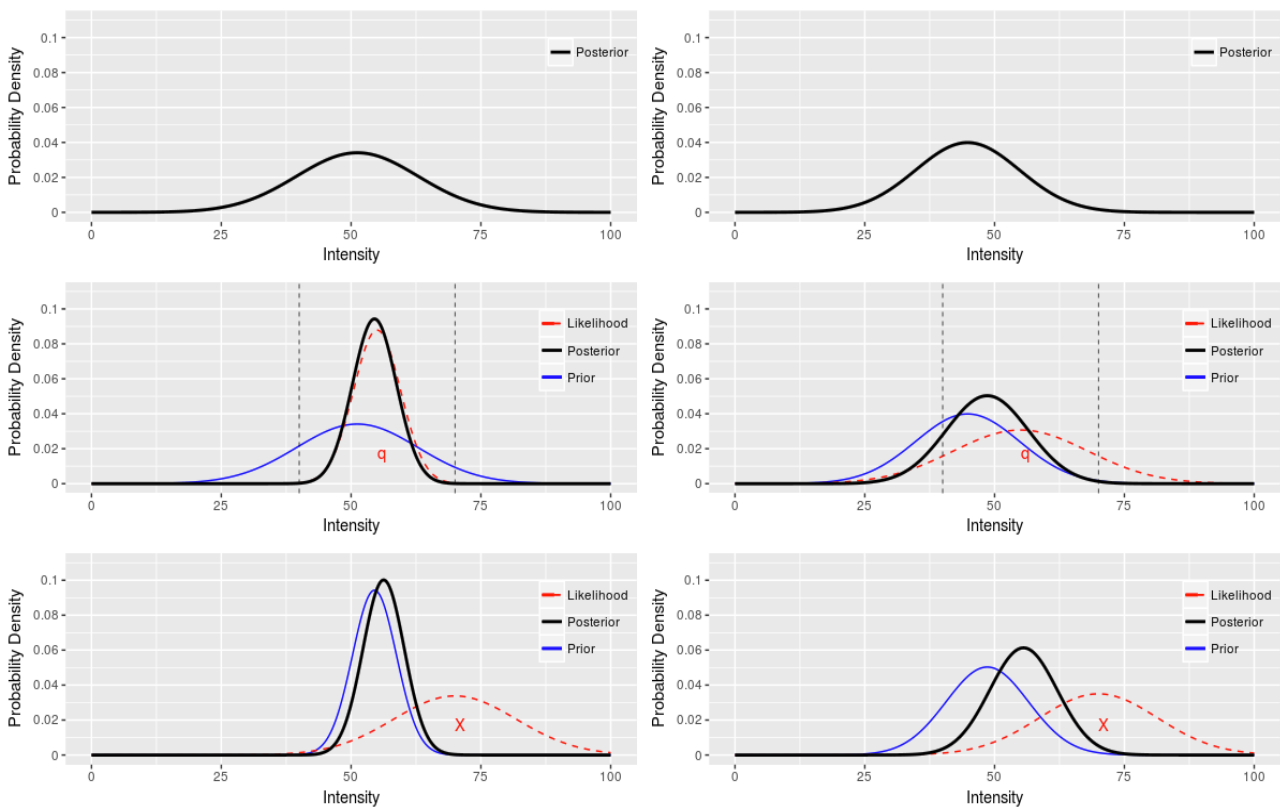
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504 Table 2 summarizes the parameter estimates achieved from fitting Model 5, the winning 'Full model'.

505 Within this perspective, the finding that the average value of ρ is of smaller magnitude than the average
506 value of β suggests that that the prior distribution for R_{ij} is biased towards the mean of the cue. These
507 parameters are inversely proportional to the strength of the cue and stimulus information when they are
508 combined to form the posterior in this model. Thus, the parameter values suggest that an increase in the
509 mean of the cue will, on average, and all other variables remaining equal, correspond to an increase in the
510 mean of the rating R_{ij} . The positive average value of η supports the hypothesis that an increase in the cue
511 variance will, on average, correspond to an increase in the variance of the prior distribution for R_{ij} and thus
512 a smaller effect of the cue on the perceived intensity, in accordance with predictive coding.

513 Table 1 also contains the DIC scores for Model 6, the 'Hierarchical model' where the model parameters
514 were allowed to vary across individual. This model fitted significantly better than all fixed-parameter
515 models (Models 1-5), suggesting that individual differences are relevant for understanding how expectation
516 influences perceived pain. Model 6 allows us to dissect a number of aspects of the psychological construct
517 of pain expectations, illustrated in Figures 2-4. Figure 2 illustrates the way in which Model 6 explains the
518 responses of two different participants in Experiment 1 to a trial where these participants were exposed to
519 the same cue. The charts on the top row illustrate the participants' cue-independent priors before (i.e.

520 either the cue or stimulus are delivered). In the middle row, the likelihood of the cue (red dashed curve) is
521 incorporated to create a posterior (black curve) which will later serve as the 'prior distribution' (blue curve),
522 $P(R_{ij}|Z_{ij})$. In the last row the 'prior distribution' (now the blue curve) is incorporated with the likelihood
523 of the stimulus (red dashed curve) leading to the posterior distribution (black curve), $P(R_{ij}|X_{ij},Z_{ij})$. The
524 left column of the figure describes a participant (participant 3) with parameters $\beta = 11.41$, $\rho = 13.05$, $\eta =$
525 0.105 , $\mu = 44.82$, and $\nu = 10.00$. The right column displays another participant (participant 4) with
526 parameters $\beta = 11.85$, $\rho = 4.54$, $\eta = 0.106$, $\mu = 51.23$, and $\nu = 11.70$. The left participant's value for ρ
527 markedly higher than that of the right participant. This causes the 'prior distribution' in the second row to
528 be markedly less precise. In the third row, this results in the posterior being closer to the actual intensity of
529 the delivered stimulus. We might characterize the behaviour displayed in the left diagram in terms of the
530 cue exerting little influence on the participant's expectation and rating. The right participant's value for ρ
531 markedly lower, which is reflected by the sharper 'prior distribution', centred around the cue mean, q_{ij} .
532 This causes the strong pull of the posterior towards the cue mean.

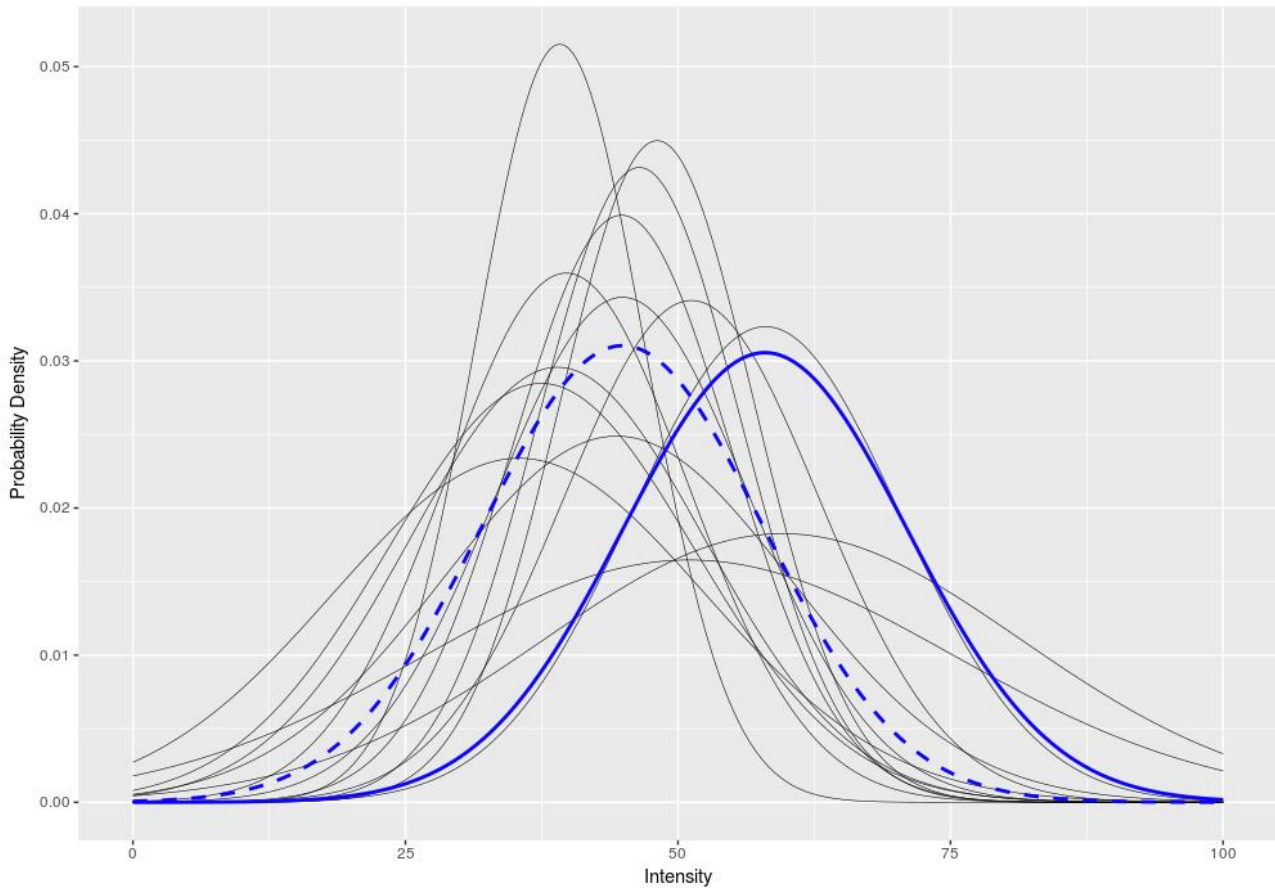


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534 **Figure 2: Illustration of the way the model explains the responses of two different participants in**
535 **Experiment 1 after exposure to the same cue.** We selected a trial in which the cue consisted of two possible
536 pain levels (4 and 7), each with 50% probability. The horizontal axis describes pain levels on a percent scale,
537 from 0 to 100. The two vertical bars indicate the possible levels of pain according to the cue (40 and 70). The
538 symbol “q” marks the mean of the expected pain, based on the cue (here, 55). The symbol “X” marks the
539 intensity X_{ij} of the delivered stimulus. Participants 3 and 4 are respectively represented in the left and right
540 columns. The top row illustrates cue-independent prior. In the middle row, the likelihood of the cue (red
541 dashed curve) is incorporated to create a posterior (black curve) which will later serve as the ‘prior
542 distribution’ $P(R_{ij}|Z_{ij})$. In the last row the ‘prior distribution’ (now the blue curve) is incorporated with the
543 likelihood of the stimulus (red dashed curve) leading to the posterior distribution (black curve),
544 $P(R_{ij}|X_{ij}, Z_{ij})$.

545

546 Figure 3 illustrates the variability in cue-independent priors among participants in Experiment 1. Here
547 the mean and standard deviation of the curves correspond with the individual parameters μ and v
548 respectively. We see that the cue-independent priors differ in location and strength leading to differences
549 in how the cue shapes the prior distribution.



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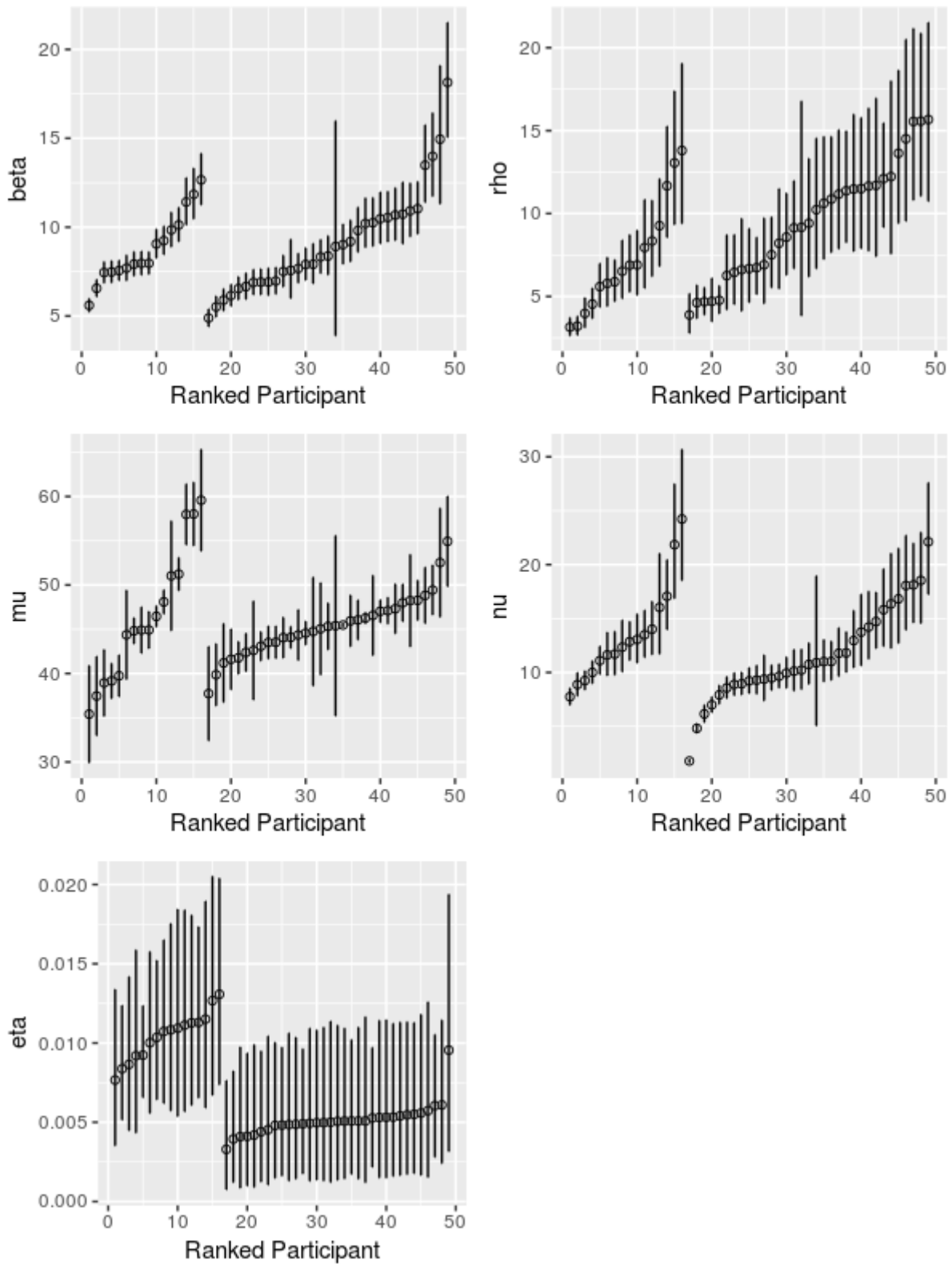
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Figure 3: Individual-level, cue-independent priors representing trait-like bias. The graphs represent the cue-independent priors for participants in Experiment 1 under the Hierarchical model (Model 6). For example, the bold blue distribution represents a participant who is more pessimistic about pain (in terms of the mean pain that they expect) than the participant represented by the dashed blue distribution. The distributions vary in both their mean and variance with the variance determining how strongly the posterior will be biased towards the mean.

Figure 4 plots the individual-specific estimates of the parameters obtained in the ‘Hierarchical model’ (Model 6) for each experiment. A clear-cut ranking of the individuals by sensitivity is evident in the plots. The estimates of parameter η appears on average to be less precise than the remaining parameters, as evident from their larger credible intervals. The individual-level estimates of the remaining parameters μ , ν , β and ρ , have narrower credible intervals, and less overlap across individuals, which suggests these

563 parameters could provide a good basis for classifying individuals. This suggests that individuals can be
564 accurately ranked on the basis of the latter set of parameters.

565



566

567 **Figure 4: Individual-level estimates for parameters in the Hierarchical model (Model 6).** There is one
568 plot per parameter (see vertical axis label). Each plot is divided in two sections, the left section reporting the
569 ranked estimates of the corresponding parameter for the participants in Experiment 1, and the right section
570 reporting the ranked estimates for the participants in Experiment 2. These estimates were obtained by
571 separately analysing the data from Experiments 1 and 2 on the basis of Model 6. Each individual in each
572 plot is represented by a circle, whose y-coordinate corresponds to the point estimate of the parameter for
573 that individual. Superimposed to each circle is the 95% Bayesian credible interval for the corresponding
574 estimate. The left (respectively, right) portion of each plot refers to Experiment 1 (respectively, 2). The
575 ordering of the individuals along the horizontal axis corresponds to their ranking by increasing value of the
576 parameter estimate.

577

578 **4. Discussion**

579 Six models of pain perception were tested using data collected from two experiments that utilised a
580 short, novel and deception-free experimental paradigm. A model comparison performed using data from
581 the first experiment supported a number of hypotheses. Firstly, it was found that modelling cue-dependent
582 priors using the mean pain intensity suggested by the cue provided a better model fit for the data than
583 using separate modal values for each intensity represented in the cue. Secondly it was found that increased
584 variance in the prior (and thus the generated expectation) decreased the influence which that prior exerted
585 on the perception of pain. Thirdly, it was shown that adding parameters that describe cue-independent
586 biases in pain perception significantly improved model fit, suggesting that such biases produce an effect on
587 pain perception that is independent of cued pain expectations. Fourthly, as the best fitting 'Full model'
588 corresponded most closely to the predictive coding framework, the results of this study lend support for
589 the predictive coding conceptualisation of pain perception. Finally, this winning model produced a
590 significantly better fit of the data when its parameters were allowed to vary at an individual level,
591 suggesting that there are substantial individual differences in sensitivity to aspects of pain expectations.
592 The results also show that this individual-level model can be used to distinguish individuals based on the

593 characteristics of their pain expectations. Importantly, the above model comparison results were replicated
594 when the analysis was repeated using data from a second experiment, a conceptual replication of the first
595 which involved an independent sample.

596 The comparison between the fits achieved by the models presented in this paper allowed us to assess
597 the viability of the predictive coding framework. The fact that Models 2 and 3 outperformed Model 1
598 replicated the typical finding the expectation can alter pain perception (e.g. Atlas & Wager, 2012; Bingel et
599 al., 2011; Colloca, & Benedetti, 2006; Peerdeman et al., 2016; Tracey, 2010). More interestingly, the fact
600 that Model 4 outperformed Model 3 confirms that the uncertainty around the expected pain value
601 modulates its influence on pain perception (Brown, Seymour, Boyle, El-Dereby, & Jones, 2008b; Colloca,
602 Petrovic, Wager, Ingvar, & Benedetti, 2010). Given that the model parameter which captures the effect that
603 variance within the cue information has on the prior (η) was found to have a positive value, it can be
604 concluded that greater uncertainty in the pain expectation decreases its effect on perception. This finding
605 aligns with predictive coding, but is in contrast to previous work which has suggested that greater
606 expectation uncertainty may increase the influence of expectation (Watkinson et al., 2013) or may increase
607 the level of perceived pain independent of the expectation (Yoshida et al., 2013). As there were many
608 discrepancies in the methodology used between these three studies, the reason for these divergent
609 findings will need to be investigated in future research. It is possible that the different types of pain stimuli
610 used (pressure by Watkinson et al., temperature by Yoshida et al.) may generate different results to those
611 achieved via the electrical pain stimulation used in the current study. Indeed, although expectations of
612 electric pain and laser pain influence ERP markers of pain delivery similarly (Hird et al., 2018), their effect
613 on neural markers of pain *anticipation* differs (Babiloni et al., 2007; Hird et al., 2018). Alternatively, as
614 Yoshida et al. used a cue which involved seeing ratings in the form of a number of 'ticks' on a visual-
615 analogue scale, such that greater uncertainty was operationalised in ticks that were more spread out, there
616 is a possibility that participants may have misinterpreted the meaning of this display, perhaps thinking that
617 a larger spread implied greater pain intensity. It is worth noting that of all the parameters in the 'Full
618 model', the estimates of parameter η appeared to be less precise than the other parameters when

619 calculated at an individual level (Figure 4.). The values of η also differed noticeable between the two
620 experiments. Therefore, further research is needed to understand exactly how expectation uncertainty
621 maps onto pain experience. Nevertheless, our results corroborate predictive coding accounts of pain
622 perception, in accordance with previous claims in favour of that framework in the same and in other
623 modalities (Clark et al., 2008; Krol & El-Deredy, 2011; Krol & El-Deredy, 2015).

624 Another finding of interest in relation to the cognitive aspects of pain expectation was that Model 5
625 outperformed Model 4, a result which suggests that cue-independent (i.e. trait-like) differences in pain
626 expectation have a significant effect on pain perception over and above the effect of cue-dependent pain
627 expectations. The way the effect of cue-independent expectations was modelled, as shaping the prior
628 distribution that was informed by the cue, was inspired by work on cognitive expectations where optimism
629 bias modulates participants' ability to learn from the information they are given (Garrett & Sharot, 2017).
630 Experimental studies of the pain perception process have often ignored the influence of expectations that
631 exist outside of those generated by the experimental paradigm, which in clinical settings are known to
632 contribute greatly to pain experience. In the case of chronic pain patients such expectations are likely to
633 contribute more to perceived pain than more cue-dependent expectations. Because pessimistic
634 expectations about procedure pain could prevent patients from taking up critical preventative treatments,
635 such as colonoscopy (Trevisani, Zelante, & Sartori, 2014) future work on pain expectation therefore needs
636 to consider the influence that individual differences in cue-independent pain expectations have on pain
637 perception.

638 While much previous research has supported the predictive coding account of pain perception (e.g.
639 Brown et al., 2008a; Brown et al., 2008b; Brown, El-Deredy, & Jones, 2014; Clark, 2013) most of this
640 previous research has been carried out at a population level, without paying attention to individual-level
641 differences in the effects of expectation. To counter this shortcoming, a version of 'Full model' was created
642 which allowed the model parameters to vary from one individual to another. This individual-variant,
643 'hierarchical' model was found to fit the experimental data significantly better than its fixed-parameter
644 equivalent, suggesting that the model and its parameters were able to characterise each individual

645 participant in terms of their sensitivity to pain expectations. This finding further suggests that these
646 parameters capture important aspects of each individual's response to pain. For example parameters ρ , η
647 and β quantify the individual's sensitivity to aspects of the cue (expectation precision, its variance, and the
648 precision of their representation of the pain stimulation). Individuals with a low value of ρ and a high value
649 of β may be more sensitive to the specific information they receive about upcoming pain, so they may be
650 more inclined to dismiss their own physical sensations in favour of expectations generated by the cue.
651 There are hints that patients with medically-unexplained pain complaints may belong to this group (Van
652 den Bergh, Witthöft, Petersen, & Brown, 2017). In a clinical setting, such individuals might benefit most
653 from psychological pain therapies that concentrate on information processing biases relating to pain, as
654 well as from training methods to increase their somatosensory sensitivity (Huque, Poliakoff, & Brown,
655 2017). In contrast, parameters μ , and ν , capture trait-like differences in pain expectation, which are
656 independent of contextual information (e.g. the cue information). The value of parameter μ specifies the
657 mean pain expected before the effect of any contextual information is considered (i.e. the cue in the
658 experimental paradigm used here) while parameter ν allows us to set apart individuals with exceptionally
659 low or high confidence in this cue-independent expectation. These cue-independent parameters can be
660 thought of as analogous to an optimism/pessimism trait relating to future pain. In a clinical setting,
661 individuals with a high value of μ and a low value of ν may be more likely to benefit from psychological pain
662 therapies that concentrate on general beliefs about pain.

663 The individual differences that the methodology presented in this paper quantifies go beyond what is
664 available through existing self-report instruments, such as the well-established pain catastrophizing scale
665 (Sullivan, Bishop, & Pivik, 1995). In chronic pain, high PCS scores are associated with reports of more severe
666 pain and reduced efficacy of physical and psychological therapies (Keefe et al., 1989). PCS and other self-
667 report measures offer a fast, reasonably accurate, but ultimately gross and subjective, description of pain
668 expectation and experience. They cannot explain what aspects of expectations drive changes in pain
669 experience. Specifically, the same score on a pain scale, given by two patients, could arise through very
670 different psychological processes. Arguably, the method to characterise individuals' sensitivity to

671 expectation described in the current paper goes further, to reveal the underlying cognitive mechanism
672 which drive the impact of expectations on pain experience. It should be acknowledged that participants in
673 the current study were not asked to report what (if any) cognitive strategies they applied during the
674 experimental task. It is therefore not possible to assess how the underlying cognitive mechanism that is
675 suggested by the model compares with participant's conscious experience of engaging in the task.

676 In this study participants were asked to rate the intensity of the pain stimulus, rather than its
677 unpleasantness, so as not to explicitly draw their attention to pain affect. Intensity, a sensory-discriminative
678 property of pain, is processed in the lateral pain system, comprising the lateral thalamus and its projections
679 to the primary and secondary somatosensory and inferior parietal cortices. In contrast, unpleasantness, an
680 affective-motivational property, is processed in the medial pain system, comprising the medial thalamus,
681 prefrontal cortex, insula and mid and anterior cingulate cortices (Bowsher 1957; Rainville et al 1997;
682 Bentley et al, 2004; Kulkarni et al 2005, 2007). It has been shown that those two systems could be activated
683 differentially by drawing attention to either the sensory or affective properties of the noxious stimulus; but
684 that they interact to create the pain experience. Specifically, top-down anticipatory effects of expectations
685 in a network comprising the affective system influence the appraisal of the sensory properties of pain
686 (Brown et al, 2014). This is highlighted by the performance of Model 5, where trait-like differences in pain
687 expectations shape the processing of the probabilistic cue, and subsequently the evaluation of the pain
688 stimulus. The proposed model provides a means of accessing the effect of this network behaviourally, at an
689 individual level.

690 The ability of the methodology described in this paper to characterise the effect of pain expectations in
691 individuals could provide useful information in assigning treatment plans if it were applied in a clinical
692 setting. As patients are likely to be differentially sensitive to expectations (Brown, El-Deredy, & Jones, 2014)
693 a method, such as the one presented in this paper, which can potentially identify which patients are most
694 sensitive to pain expectations, and which facets of pain expectations they are sensitive to, could help
695 inform clinical decisions. For example, pain expectations are a key target in non-pharmacological therapies
696 for pain, such as Cognitive Behavioural Therapy (CBT). CBT is effective in reducing chronic pain and pain-

697 related disability partly because it changes patients' pain expectations (Bingel et al., 2011). Unfortunately,
698 CBT is not as effective as we would wish: more than half of patients with chronic pain do not benefit from
699 CBT (Peerdeman et al., 2016; Smith et al., 2016; de Williams, Eccleston, & Morley, 2012). Put simply, if a
700 patient can be identified as being biased to report stronger pain they may be a better candidate for CBT
701 than a patient who reports the delivered pain more accurately; and their specific expectation sensitivity
702 profile can further improve the specific therapeutic intervention. It is hoped that the method described in
703 this paper may ultimately prove useful in selecting suitable candidates for pain management treatment,
704 adding quantitative information that is less affected by introspective limitations to existing self-report
705 questionnaires that assess pain expectations. This could facilitate the personalisation of treatment
706 selection, an approach that is particularly important in the current climate when health services are
707 stretched, and access to effective treatment is limited (Enck et al., 2013). In addition to providing input to
708 clinical decisions, the methodology presented here could also be used in clinical trial research to attempt to
709 control for placebo effects when selecting control and experimental groups. To further the goal of
710 providing a clinical tool using our approach, the current research needs to be repeated in a variety of
711 clinical pain populations. Such work would be required in order to establish the clinical relevance of the
712 individual parameters of pain expectations that have been established in this study.

713 Prior to clinical validation, it would be beneficial for the model and associated methodology to be tested
714 further on non-clinical samples. The samples used in the current experiments were modest in size and were
715 derived from a relatively homogenous population (undergraduates). A large-scale validation and replication
716 of the model and associated methodology with a more varied non-clinical population would therefore be
717 welcome. In addition to simply validating the model, such work could also be used to answer empirical
718 questions relating to the model variables. For example, it would be of interest to understand whether the
719 model variables are stable over time within the same individual, and how the model variables vary within
720 the same individual depending on the type of pain stimulation used (e.g. laser vs electrical) and the
721 anatomical location of the stimulation. Investigations of other non-clinical determinants of pain experience
722 (e.g. cultural differences, differences due to prior exposure to pain) could also be performed. In addition,

723 although trial order was randomised for each participant to prevent systematic influences due to across
724 trial learning effects, there is scope for future exploration of learning patterns. It would be interesting, for
725 example, to examine whether the participant's experience up to and including trial $t - 1$ influences the
726 outcome on trial t . Such work would inform any clinical application of the model, while also providing more
727 general insight into human pain perception.

728 One limitation of our design is that the pain intensity participants received was, on average, not very
729 different from the pain intensity that they had expected. This may be important, because key aspects of
730 predictive coding resemble the assimilative part of assimilation-contrast theory (Hoyland, Harvey, & Sherif,
731 1957), which predicts that the distance between prior and the physical stimulus is crucial. Both theories
732 agree that when the distance is small, namely, when the input is not too discrepant from our existing
733 anchor, we will assimilate it and our experience will reflect a 'compromise' between the reality and our
734 expectations. However, when the reality is very different to our expectations assimilation-contrast theory
735 predicts that we will experience the real, discrepant stimulus as even more discrepant compared to our
736 expectations. Our data does not currently allow us to decide whether pain experiences show such contrast
737 effects. An additional limitation of our design is that we are currently not able to distinguish between
738 participants who rated what they 'really felt' and participants who rated their pain as closer to the values of
739 the cue because of demand characteristics. The possible influence of demand characteristics is prevalent in
740 studies of pain experience across paradigms, including placebo designs and cue-based designs, so this
741 caveat is not unique to our design. Future experiments using our experimental paradigm could explore this
742 issue further, for example by manipulating the working memory load of participants, which reduce goal-
743 directed behaviour (Otto, Gershman, Markman, & Daw, 2013). We should also emphasise that our
744 selection of an "optimal" model has been guided by statistical criteria, a necessary requirement to achieve
745 useful prediction of population behaviour. However, the extent to which the model reflects cognitive
746 processes, as well as particular theories such as the predictive coding framework, should be tested further
747 through experimental manipulations of the relevant cognitive and computational processes.

748 In summary, model comparison and validation yielded a number of important findings. The predictive
749 coding framework was shown to provide an accurate description of pain perception. In particular the
750 framework's predictions relating to the effect of expectation uncertainty were supported. Trait-like pain
751 expectations that exist independent of any cued pain information were shown to have an influence on pain
752 perception that was separate and distinguishable from those provided by cued pain expectations. Finally
753 the methodology presented in this paper was able to characterise an individual's sensitivity to pain
754 expectations, potentially providing the basis for a clinical tool that could guide practitioners who deliver
755 individual psychological pain management interventions.

756 **Acknowledgements**

757 CB was partially supported by the FP7 MIMOmics European Collaborative Project, as part of the
758 HEALTH-2012-INNOVATION scheme and by the Medical Research Council. RH and DT were partially
759 supported by ESRC First Grant ES/I010424/1. WED acknowledges the support of CONICYT, Chile, FONDECYT
760 project 1161378 and Basal project FB0008. We thank A. Jones for inspiring this project, N. Begum and E.
761 Hird for helpful suggestions, and A. Sparkes for collecting some of the data reported in this paper.

762 All authors declare no conflict of interest.

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924 **Supplementary material**

925 **Supplementary Table 1:** Voltage delivered for each subjective pain level in Experiments 1 and 2.

Voltage (in Volts) delivered for each subjective pain level		
Pain Level	Experiment 1: Mean(SD)	Experiment 2: Mean(SD)
Pain Level 3	1.34 (.46)	1.59 (.17)
Pain Level 4	1.69 (.51)	1.90 (.20)
Pain Level 5	2.03 (.61)	2.23 (.22)
Pain Level 6	2.35 (.67)	2.56 (.25)
Pain Level 7	2.74 (.84)	2.90 (.29)

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Supplementary Table 2: Trial types in Experiment 1.

Possible pain levels, depicted in the cue (their probabilities)	Mean expected pain	Delivered pain levels	Size of Prediction error at pain delivery	Number of repetitions per block
Cues with 1 option				
3 (100%)	3	3	0	1
4 (100%)	4	4	0	1
5 (100%)	5	5	0	1
6 (100%)	6	6	0	1
Cues with 2 options				
4 (50%)	4.5	4	-0.5	1
5 (50%)		5	+0.5	1
3 (25%)	4.5	3	-1.5	1
5 (75%)		5	+0.5	3
4 (75%)	4.5	4	-0.5	3
6 (25%)		6	+1.5	1
5 (50%)	5.5	5	-0.5	1
6 (50%)		6	+0.5	1
4 (25%)	5.5	4	-1.5	1
6 (75%)		6	+0.5	3
5 (75%)	5.5	5	-0.5	3
7 (25%)		7	+1.5	1
Cues with 4 options				
3 (25%)	4.5	3	-1.5	1
4 (25%)		4	-0.5	1
5 (25%)		5	+0.5	1
6 (25%)		6	+1.5	1
4 (25%)	5.5	4	-1.5	1
5 (25%)		5	-0.5	1
6 (25%)		6	+0.5	1
7 (25%)		7	+1.5	1

929 *Note.* 16 trial types correspond to a 2 (Expected pain level: 4.5, 5.5) x 2 (Discrepancy of expectations
 930 from delivered pain: 0.5,1.5) x 2 (Direction of discrepancy: positive, negative) x 2 (The number of possible
 931 pain levels participants could expect: 2, 4). In order to implement this design, 4 additional trial types were
 932 included; those are presented in light shaded boxes. For the purpose of a manipulation check, 4 further trial
 933 types with 100% probability of receiving a particular pain level were also included, presented in dark
 934 shaded boxes.

935

936 **Supplementary Table 3.** Trial types in Experiment 2.

Possible pain levels, depicted in the cue (their probabilities)	Mean expected pain	Delivered pain level	Size of prediction error at pain delivery
Cues with 1 option			
3 (100%)	3	3	0
4 (100%)	4	4	0
5 (100%)	5	5	0
6 (100%)	6	6	0
Cues with 2 options			
4 (50%)	4.5	4	-0.5
5 (50%)		5	+0.5
3 (50%)	4.5	3	-1.5
6 (50%)		6	+1.5
5 (50%)	5.5	5	-0.5
6 (50%)		6	+0.5
4 (50%)	5.5	4	-1.5
7 (50%)		7	+1.5
4 (50%)	5	4	-1
6 (50%)		6	+1
3 (50%)	5	3	+2
7 (50%)		7	-2

937 *Note.* 8 trial types correspond to a 2 (Expected pain level: 4.5, 5.5) x 2 (Discrepancy of expectation from
938 delivered pain: 0.5, 1.5) x 2 (Direction of discrepancy: positive, negative). 4 trial types presented in shaded
939 boxes correspond to a 2 (discrepancy of expectations from delivered pain) x 2 (direction of discrepancy:
940 positive, negative). 4 further trial types where cues offered 100% certainty about the impending pain level
941 were included for the purpose of a manipulation check. All trial types were delivered once per block.

942 **Supplementary Table 4:** Rated pain experience for cues with 100% certainty in Experiments 1 and 2.

Descriptive statistics for ratings of 100% chance trials at each pain level		
Pain level	Experiment 1: Mean (SD)	Experiment 2: Mean (SD)
Pain level 3	24.30 (8.47)	26.43 (15.92)
Pain level 4	36.96 (10.37)	35.25 (15.16)
Pain level 5	49.96 (13.47)	44.59 (14.80)
Pain level 6	60.99 (16.76)	52.72 (15.96)

943 **Note: Mean (SD) of ratings on a scale of 1-100**

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946 **Appendix**

947 **Derivation 1:** Derivation of the ‘prior distribution’

948 Here we derive $P(R_{ij}|Z_{ij})$ as resulting from a Bayesian updating process and motivate its use as the
949 ‘prior distribution’. Following from Bayes’ theorem, the ‘prior distribution’ is proportional to the product of
950 a cue-independent prior and a likelihood function of the cue:

951
$$P(R_{ij}|Z_{ij}) \propto P(Z_{ij}|R_{ij}) \times P(R_{ij})$$

952 We choose the cue-independent prior to take the form:

953
$$P(R_{ij}) = (2\pi v)^{-\frac{1}{2}} \exp\left(-\frac{1}{2v^2} (R_{ij} - \mu)^2\right)$$

954 This prior is independent of the cue, and represents a stable, trait-like bias to expect pain of a certain
955 intensity. Higher values of parameter μ (the mean of the cue-independent prior) reflect the expectation of
956 higher levels of pain, independent of any cue information. Higher values of parameter v (the standard
957 deviation of the cue-independent prior) reflect greater uncertainty (and therefore lesser influence) of this
958 cue-independent prior. Participants with high μ and low v can be thought of as pessimistic about pain.

959 We choose the likelihood function of the cue to take the form:

960
$$P(Z_{ij}|R_{ij}) \propto (2\pi * (\rho + \eta \times sd_{ij}))^{-\frac{1}{2}} \exp\left(-\frac{1}{2 * (\rho + \eta \times sd_{ij})^2} (q_{ij} - R_{ij})^2\right)$$

961 This likelihood function incorporates two parameters which will eventually modulate the effect of the
962 cue information Z_{ij} on the likelihood of the rating R_{ij} . The parameter ρ controls the variance of the
963 likelihood function generated by the cue. In effect it represents the precision of this prior. In contracts η
964 dictates the influence the cue’s variance has on the sharpness of the likelihood function. Together these
965 parameters determine the extent to which the cue information modulates the prior distribution, and thus
966 the subsequent experience of pain. The influence of the cue increases with lower values of ρ and η .

967 Plugging these functions back into the original equation and now conditioning on Z_{ij} we can express
968 the prior distribution as:

$$969 P(R_{ij}|Z_{ij}) \propto \text{Normal}(q_{ij}, \rho + \eta \times sd_{ij}) \times \text{Normal}(\mu, v)$$

970

971 **Derivation 2:** Incorporation of the Likelihood of the Stimulation

972 The posterior is given, up to a proportionality constant, by the product of the prior and the likelihood of
973 the stimulation:

$$974 P(R_{ij}|X_{ij}, Z_{ij}) \propto P(X_{ij}|R_{ij}, Z_{ij}) \times P(R_{ij}|Z_{ij})$$

975 We take the likelihood of the stimulation to factor into two components, $P(X_{ij}|R_{ij}, Z_{ij}) = f_1(X_{ij}, R_{ij}) \times$
976 $f_2(X_{ij}, Z_{ij})$. Since we consider the posterior only up to a proportionality constant, we are only concerned
977 with the $f_1(X_{ij}, R_{ij})$ component which we take to be normally distributed:

$$978 f_1 = (2\pi\beta)^{-\frac{1}{2}} \exp\left(-\frac{1}{2\beta^2}(X_{ij} - R_{ij})^2\right)$$

979 with $\beta > 0$. Each predicted value of R_{ij} is compared with the external sensory information, associating each
980 such value with a measure of 'surprise', which our model takes to increase with an increasing distance
981 between R_{ij} and the actual intensity of the stimulation, X_{ij} . The value of β determines the extent that the
982 perceptual mechanism will tolerate a given disparity between the predicted experience and the actual
983 sensation, with smaller values of β implying greater sharpness of the likelihood function around X_{ij} and
984 hence a reduced tolerance.

985 Plugging f_1 back into the original equation and now conditioning on X_{ij} we can express the posterior
986 distribution as:

$$987 P(R_{ij}|X_{ij}, Z_{ij}) \propto \text{Normal}(X_{ij}, \beta) \times P(R_{ij}|Z_{ij})$$