Boundary effects of expectation in human pain perception

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Abstract

Perception is the result of both expectation and sensory stimulation. This is reflected in placebo analgesia, where expecting low pain leads a painful stimulus to feel less painful. Yet it is maladaptive for a highly erroneous expectation to result in an unrealistically low pain experience. We hypothesised that in estimating the intensity of a painful stimulus which is preceded by a very discrepant expectation, the perception is influenced less by the expectation. We modelled the reported pain intensity as a function of the prediction error. We used linear mixed modelling on two independently collected pain cueing datasets, the second of which was preregistered (osf.io/5r6z7). Reported pain intensities were best explained by a quartic polynomial model of the prediction error, indicating the influence of expectations on perceived pain decreased when pain was highly discrepant to expectation, suggesting that the size of prediction error has a functional role in pain perception.

Introduction

The experience of pain results from the integration of the actual sensory reality with prior expectations about how the pain will feel. Expectations about an upcoming painful event shift the perceived intensity of pain closer to the expected intensity. For example, in placebo analgesia, expecting low pain decreases pain perception and associated brain activity (Colloca, Wager, 2004; Watson, El-Deredy, Vogt, & Jones, 2007; Sigaudo, & Benedetti, 2008; Tracey, 2010; Büchel, Geuter, Sprenger, & Eippert, 2014; Wager & Atlas, 2015). Likewise, expecting high pain increases the perceived intensity of pain, as in nocebo hyperalgesia (Blasini, Corsi, Klinger, & Colloca, 2017).

Imagine having a calm picnic in the garden, when you are suddenly stung by a bee. You expected no pain at all, but are immediately overwhelmed by searing pain. This is an example for a large discrepancy between expectation and sensory evidence, termed prediction error (PE). Evidence clearly indicates that experiencing large PEs leads to learning over time (Li & McNally, 2014; McHugh, Barkus, Huber, Capitão, Lima, Lowry, & Bannerman, 2014; Vlaeyen, 2015). However, it is not clear whether the magnitude of the prediction error has any immediate functional role in the evaluation of a current stimulus. Although it is adaptive for expectations to modulate its perception (Jonas, Crawford, Colloca, Kaptchuk, Moseley, Miller, Kriston, Linde, & Meissner, 2015), failing to adjust perception based on the immediate sensory reality could lead to inaccurate, possibly hallucinatory perception, as described in theories of psychosis (Sterzer, Adams, Fletcher, Frith, Lawrie, Muckli, Petrovic, Uhlhaas, Voss, & Corlett, 2018). In non-psychotic individuals, when prediction error is high, it would be adaptive to decrease the influence of expectation on perception, or even ignore expectations altogether. Based on these considerations we hypothesised that there should an observable boundary to the modulation of pain perception by expectation when individuals are presented with increasingly discrepant sensory evidence. To test this hypothesis we delivered pain stimulus intensities that violated cued expectations to increasing degrees and tested the effect on the resulting pain intensity rating.

We parametrically model the influence of cued intensity and stimulus intensity on pain rating, and predict that on Trials with highly unexpected pain stimulus intensities – and a large PE - the weight of cued intensity on pain intensity rating will decrease. The magnitude of PE was defined as the numerical discrepancy between cued intensity and stimulus intensity on a given Trial. The outcome variable is the difference between the stimulus intensity and the pain rating the participant gives, which we term subjective error, or PE_{sub}. A small PE_{sub} indicates a rating close to the actual stimulus intensity, whereas a large PE_{sub} suggests the rating was influenced by factors other than the incoming stimulus intensity. PE_{sub} provides a measure of how much pain intensity ratings were influenced by the cue on a Trial-by-Trial basis. A non-monotonic relationship between PE and PE_{sub} could indicate that cued intensity influenced pain intensity rating up to a certain threshold, reflected in an increase in

PE_{sub}, and that this influence decreased when stimulus intensity was highly unexpected, reflected in a decrease in PE_{sub}. This would suggest that there is a 'tipping point' where pain stimulation intensity is so discrepant to expectation that the influence of expectations on perceived pain intensity decreases (Schematic figure 1). As Figure 1 shows, we tested for this in the context of pain that is greater than expected (positive PE, on the right side of the figure), as well as in the context of pain that is lower than expected (negative PE, on the left side of the figure). We further validated this prediction by collecting a second, independent dataset and repeating our analysis, and by implementing a second, more complex analysis examining possible changes in the effect of expectations throughout the course of the session. The second dataset and accompanying analysis were preregistered (osf.io/5r6z7).

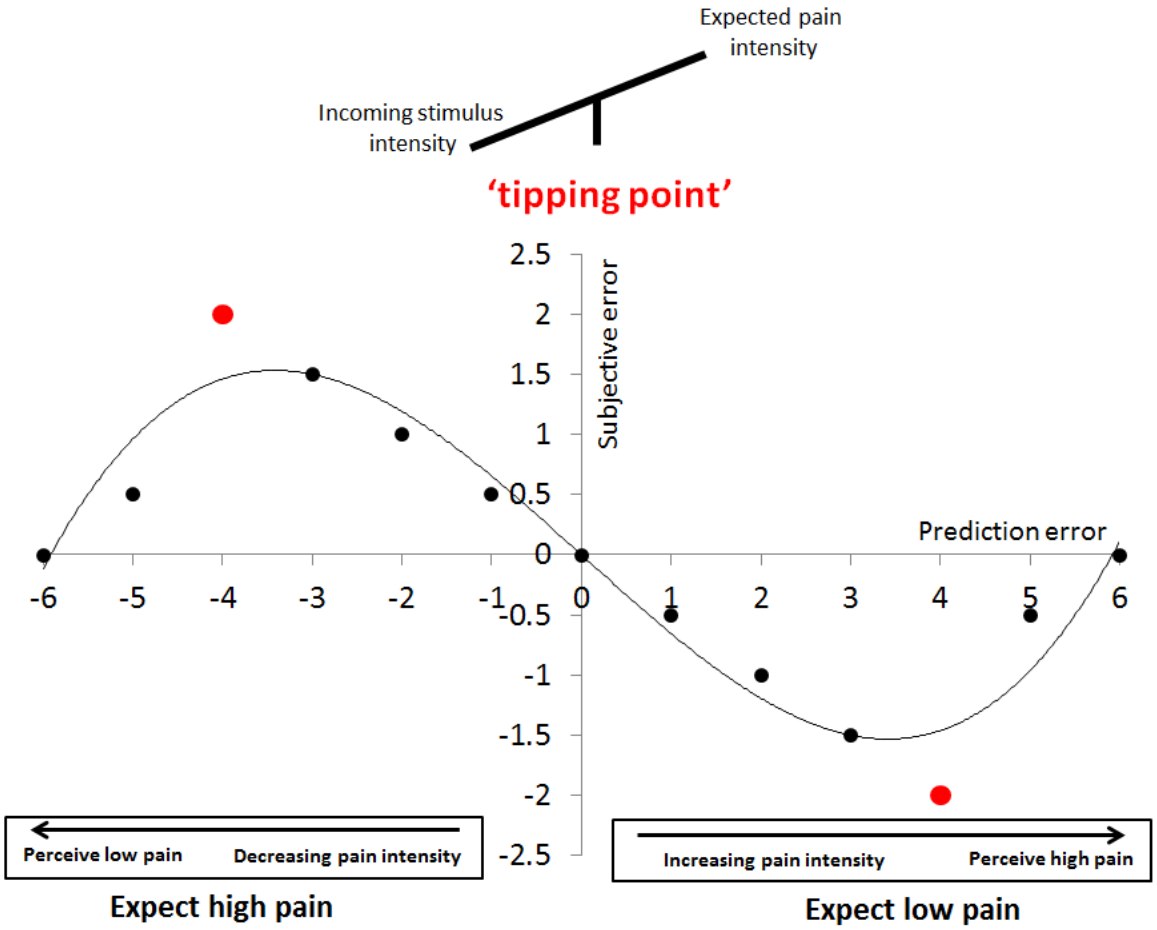

Figure 1. *Graphical representation of the hypothesised polynomial relationship between PE and* PE_{sub}*. As the discrepancy between cued intensity and stimulus intensity (PE) increases (from the origin towards both extremes of the X axis), the discrepancy between stimulus intensity and pain intensity rating (*PE_{sub}*) also increases, as expectations influence pain perception. The 'tipping point' (red marker) is reached where stimulus intensity is so unexpected that the influence of expectations begins to decrease. Positive PE, where pain was greater than expected, is plotted on the right side of the plot. For example, a PE of +2 would reflect a cued expectation of 2 on the NPS, but an actual stimulus intensity of 4 NPS (4 NPS – 2 NPS); as this is a small PE, the cued expectation influences perception, resulting in a perception of 3 NPS and a* PE_{sub} *of -1 (3 NPS – 4 NPS). A PE of +5 would reflect the same cued intensity, 2 NPS, but an actual stimulus intensity of 7 NPS; as this is a large PE, beyond the perceptual 'tipping point', the influence of expectation on perceived pain is decreased, resulting in a perception of 6.5 NPS, and* PE_{sub} *is decreased to -0.5 (6.5 NPS – 7 NPS). This hypothetical relationship is also plotted for pain that is lower than expected pain, associated with negative PE, on the left side of the plot. Across positive and negative PE Trials, the hypothesised relationship between PE and* PE_{sub} *would be best expressed by a cubic polynomial.*

Materials & Methods

Participants

For both Dataset 1 and 2, participants aged 18-35 were recruited via university advertisements. Participants received £15 compensation. Participants had normal or corrected-to-normal vision. They had no history of neurological or psychiatric conditions, had not taken analgesics on the day of the experiment, and did not have a history of chronic pain. Ethical approval was granted by the University of Manchester, where the study took place. For Dataset 1, 31 participants aged 18-35 (19 females, mean age 23 years), and for Dataset 2, 30 participants (15 females, mean age 21 years) were recruited into the study. For Dataset 1 we determined an appropriate sample size of 30 subjects by examining previous studies investigating the effect of expectation on electrical pain and more subtle effects such as the effect of certainty or subliminally presented cue on pain intensity rating, which typically recruit 15-30 participants (Brown, Seymour, El-Deredy, & Jones, 2008; Colloca & Benedetti, 2006; Jensen, Kaptchuk, Kirsch, Raicek, Lindstrom, Berna, Gollub, Ingvar, & Kong, 2012). Sample size for Dataset 2 was based on that of Dataset 1. The two studies only differed in terms of the experimenter collecting the data, and the room the data were collected in, which were nonetheless similar in shape, size and light level. They took place approximately 9 months apart.

Apparatus

Visual stimuli were presented on a desktop computer screen one metre away from the participant. Painful stimuli were electrical pulses delivered via a concentric electrode by a constant current stimulator (Digitimer DS5 2000, Digitimer Ltd., Welwyn Garden City, UK). The pulse width of the electrical stimulation was 5 milliseconds. All stimuli were controlled through a Matlab platform (Mathworks) which interfaced with the pain stimulator via a digital-to-analogue convertor (Multifunction I/O device, National instruments, Measurement House, Berkshire, UK). Participants submitted their intensity ratings of the pain using a keypad.

Procedure

Upon arrival to the lab, participants were briefed by the experimenter, who introduced the study as a straightforward test of pain perception. After providing consent, participants washed both hands with soap and water.

Participants first underwent a pain calibration procedure on their left hand to determine their response to increasing electrical stimulus intensities. The first stimulus was at a low intensity which is below the threshold for pain perception in most people. The stimulus intensity increased in a ramping procedure up to a maximum of five volts. We used a 0-10 Numerical Pain Scale (NPS) to measure the pain intensity rating, where a pain intensity rating of NPS 2 was when the stimulus became “just

painful", NPS 5 was "medium pain", and NPS 8 was at the point where stimulus was "just tolerable", replicating previous research (Atlas, Wielgosz, Whittington, & Wager, 2014). We repeated this procedure three times and computed the average stimulus intensities over these three repetitions corresponding to NPSs 2, 3, 4, 5, 6, 7 and 8. Participants then underwent a pre-experiment test procedure: stimulus intensities corresponding to their pain intensity ratings NPS 2 to 8 were delivered in a pseudorandom order four times and participants were instructed to identify the intensity of each pulse. Participants had to correctly identify 75% of stimulus intensities to continue to the main experiment. If they did not achieve this in the test procedure, the intensities were adjusted (intensity was increased if participants rated the stimulus intensity as lower than in the pain calibration procedure, and vice versa), and the test repeated until participants correctly identified 75% of stimulus intensities.

In the main experiment, participants were instructed that the cue predicted the stimulus intensity on each Trial. The cue was a number on the computer screen which depicted the intensity of upcoming stimulation (Figure 2), and then a stimulus intensity was delivered which either corresponded to the cued intensity or violated it at varying levels, in a partially reinforced cueing procedure (Table 1). Only the NPS 2 ("just painful") and NPS 8 ("highest tolerable pain") cues were followed by unexpected stimulus intensity (58% of Trials); all other pain cues were veridical (the cued intensity matched the stimulus intensity) (42% of Trials). The veridical Trials reinforced participant's belief in the validity of the cues.

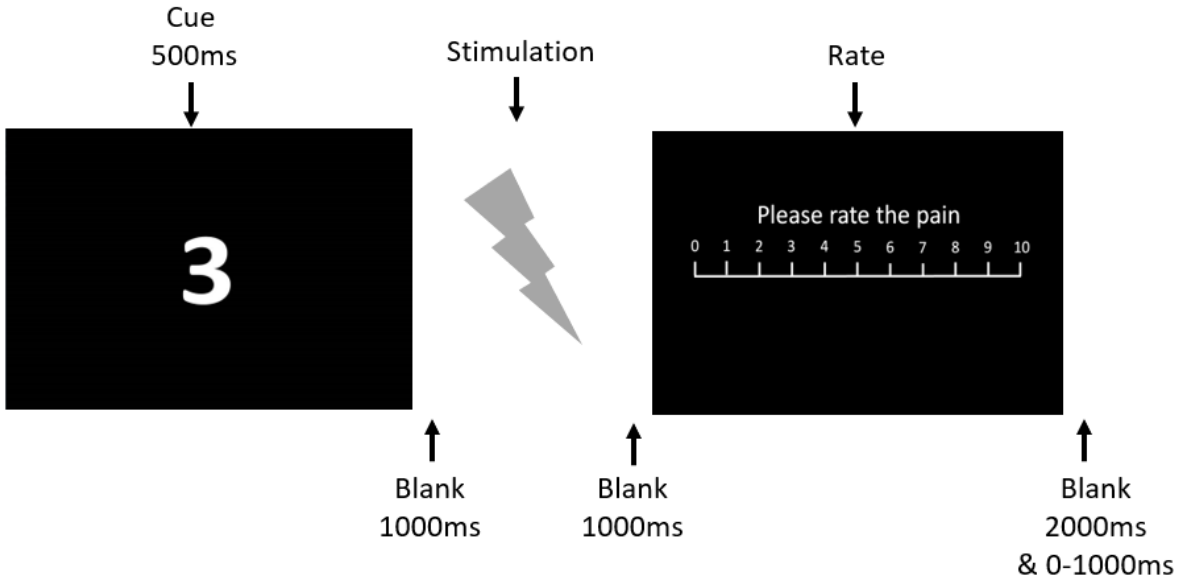

Figure 2. *Trial timeline. After viewing a fixation cross, participants viewed a number from 2 to 8 which depicted the cued intensity for that Trial. After a blank screen, participants received the stimulus, followed by another blank screen. A rating screen was presented which prompted participants to rate the pain on a NPS scale..*

The cue depicted a cued intensity of NPS 2, 3, 4, 5, 6, 7 or 8 (figure 2 and table 1). In PE Trials, after presentation of the cued intensities 2 or 8, participants could actually receive any of the 2, 3, 4, 5, 6, 7 or 8 of stimulus intensity. Thus a range of PEs could be elicited. Participants were instructed to rate the intensity of the stimulus and were not informed that the cues were discrepant. See table 1 for a summary of all Trials in the study.

Table 1: *A summary of all Trials*

Cued intensity	Stimulus intensity	PE	Number of Trials
2	2	0	5
2	3	1	5
2	4	2	5
2	5	3	5
2	6	4	5
2	7	5	5
2	8	6	5
3	3	0	10
4	4	0	10
5	5	0	10
6	6	0	10
7	7	0	10
8	8	0	5
8	7	-1	5
8	6	-2	5
8	5	-3	5
8	4	-4	5
8	3	-5	5
8	2	-6	5

On each experimental Trial, participants viewed a fixation cross, a cue, and then a blank screen. The stimulus was delivered, and a screen was presented which prompted participants to numerically rate their perceived pain intensity on a 0-10 NPS using a keypad. There was no time limit on this response. See figure 2.

Data analysis

We aimed to test whether PE_{sub} expressed a relationship with PE. We analysed pain intensity ratings to stimuli which had a cued intensity of NPS 2 (low pain) or NPS 8 (high pain). PE was calculated as the numerical difference between the cued intensity and the stimulus intensity on a given Trial, and so ranged from -6 (cue NPS 8 pain, deliver NPS 2 pain) to +6 (cue NPS 2 pain, deliver NPS 8 pain). This provided a measure of how discrepant the stimulus intensity was compared with expectation. PE_{sub} was calculated as the numerical difference between the stimulus intensity and the pain intensity rating

on a given Trial. This provided a measure of how far expectations shifted the pain intensity rating away from the stimulus intensity.

A cubic polynomial model was initially fitted to Dataset 1 to test our hypothesis of a non-monotonic relationship between PE and $PE_{sub.}$ To investigate whether Trial influenced the cubic relationship, we also implemented a more complex analysis where we included the effect of Trial and interaction between PE and Trial. In this more complex model we included a 4th order term which was motivated by the observation that in some of the participants in Dataset 1, a quartic curve was expressed (Figure 6, Supplementary Materials). Then we collected a second, independent dataset, to test whether the predicted relationship would be replicated.

Basic Model

The following cubic polynomial model was initially fitted to analyse the relationship between PE and PE_{sub}:

$$\mathrm{PE}_{\mathrm{sub}ij} = \beta_0 + \beta_1 \mathrm{PE}_{ij} + \beta_2 \mathrm{PE}_{ij}^2 + \beta_3 \mathrm{PE}_{ij}^3 + \varepsilon_{ij}\,, \qquad i = 1, \dots, m;\ j = 1, \dots, n_i$$

where $\mathrm{PE}_{\mathrm{sub}ij}$ corresponds to PE_{sub} for the j^{th} observation of the i^{th} participant, PE_{ij} is PE for the j^{th} observation of the i^{th} participant, m is the number of participants in study and n_i is the number of Trials for the i^{th} participant. We also assume that $\varepsilon_i = \left(\varepsilon_{i1}, \dots, \varepsilon_{in_i}\right)^T \sim N_{n_i}(0, \sigma^2 I_{n_i})$, with unknown variance σ^2, that is one residual variance for each participant and for each trial.

Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values were calculated for each model to allow for model comparison.

To further investigate any effect of Trial in the data which could influence the cubic relationship and account for the more subtle relationship seen in Dataset 1 (figure 4), we next implemented a more complex analysis which included a 4th order term and the effect of Trial and interaction between PE and Trial. The inclusion of trial was motivated by the observation that sensitivity to painful stimulation can vary over time (Bingel, Schoell, Herken, Büchel, & May, 2007). In support of this, in Dataset 1, across all Trials, Trial number negatively correlated with pain intensity rating, suggesting that pain intensity rating habituated over time (B = -.*002*, SE = .001, p=0.03, 95% CI =-.004, -.0003). Furthermore, experiencing PEs could, over time, change participant's association between the cue and the pain outcome (Li & McNally, 2014; McHugh, Barkus, Huber, Capitão, Lima, Lowry, & Bannerman, 2014; Vlaeyen, 2015). Because including these effects resulted in a complex model, the second dataset and accompanying analysis were preregistered (osf.io/5r6z7).

Complex model

The following linear mixed effects model was fitted to analyse the relationship between PE and PE_{sub}:

$$\begin{aligned} \mathrm{PE}_{\mathrm{sub}ij} = \beta_0 + \beta_1 \mathrm{PE}_{ij} + \beta_2 T_{ij} + \beta_3 \mathrm{PE}_{ij}^2 + \beta_4 \mathrm{PE}_{ij}^3 + \beta_5 \mathrm{PE}_{ij}^4 + \beta_6 \mathrm{PE}_{ij} T_{ij} + \beta_7 \mathrm{PE}_{ij}^2 T_{ij} + \beta_8 \mathrm{PE}_{ij}^3 T_{ij} \\ + \beta_9 \mathrm{PE}_{ij}^4 T_{ij} + b_{1i} + b_{2i} \mathrm{PE}_{ij} + \varepsilon_{ij}\,, \qquad i = 1, \dots, m;\ j = 1, \dots, n_i \end{aligned}$$

Notation here is similar to the basic model; additionally, we denote T_{ij} as the Trial number for the j^{th} observation of the i^{th} participant and, b_{1i} and b_{2i} as the random intercept and random slope for PE. The model includes polynomial terms in PE up to 4^{th} order, a linear effect for Trial and all two-way interactions between the PE polynomial terms and Trial. Interactions can be interpreted as changes in the overall relationship between PE and PE_{sub} in different Trials. To see the effect of Trial more clearly, we can rearrange the model above in the following way:

$$\begin{aligned} \mathrm{PE}_{\mathrm{sub}ij} = \overbrace{(\beta_0 + \beta_2 T_{ij})}^{\alpha_0} + \overbrace{(\beta_1 + \beta_6 T_{ij})}^{\alpha_1} \mathrm{PE}_{ij} + \overbrace{(\beta_3 + \beta_7 T_{ij})}^{\alpha_2} \mathrm{PE}_{ij}^2 + \overbrace{(\beta_4 + \beta_8 T_{ij})}^{\alpha_3} \mathrm{PE}_{ij}^3 \\ + \overbrace{(\beta_5 + \beta_9 T_{ij})}^{\alpha_4} \mathrm{PE}_{ij}^4 + b_{1i} + b_{2i} \mathrm{PE}_{ij} + \varepsilon_{ij} \end{aligned}$$

This shows that as the Trial number (T_{ij}) increases, the coefficients of the polynomial PE terms $\alpha_0, \alpha_1, \alpha_2, \alpha_3, \alpha_4$ increase (decrease) if $\beta_2, \beta_6, \beta_7, \beta_8, \beta_9$ are positive (negative). The above formulation also indicates that the random intercept b_{1i} accounts for differences in the intercept α_0 (this is the value of PE_{sub} when PE=0) for each participant, whereas the random slope b_{2i} allows a different linear effect of PE, i.e. $\alpha_1 + b_{2i}$, for each participant. The following assumptions are made about the random intercept and random slope for PE, as well as the measurement errors:

$$b_i = (b_{1i}, b_{2i})^T \sim N_2(0, G) \quad \text{and} \quad \varepsilon_i = \left(\varepsilon_{i1}, \dots, \varepsilon_{in_i}\right)^T \sim N_{n_i}(0, R),$$

where G and R are unknown covariance matrices.

AIC and BIC values were calculated for each model to allow for model comparison

Results

The plot of averaged pain ratings from Dataset 1 suggested that as stimulus intensity increased, pain intensity rating increased (figure 3). As expected, a stimulus preceded by a level 2 cue (black) was rated as lower than the same intensity stimulus preceded by a level 8 cue (grey).

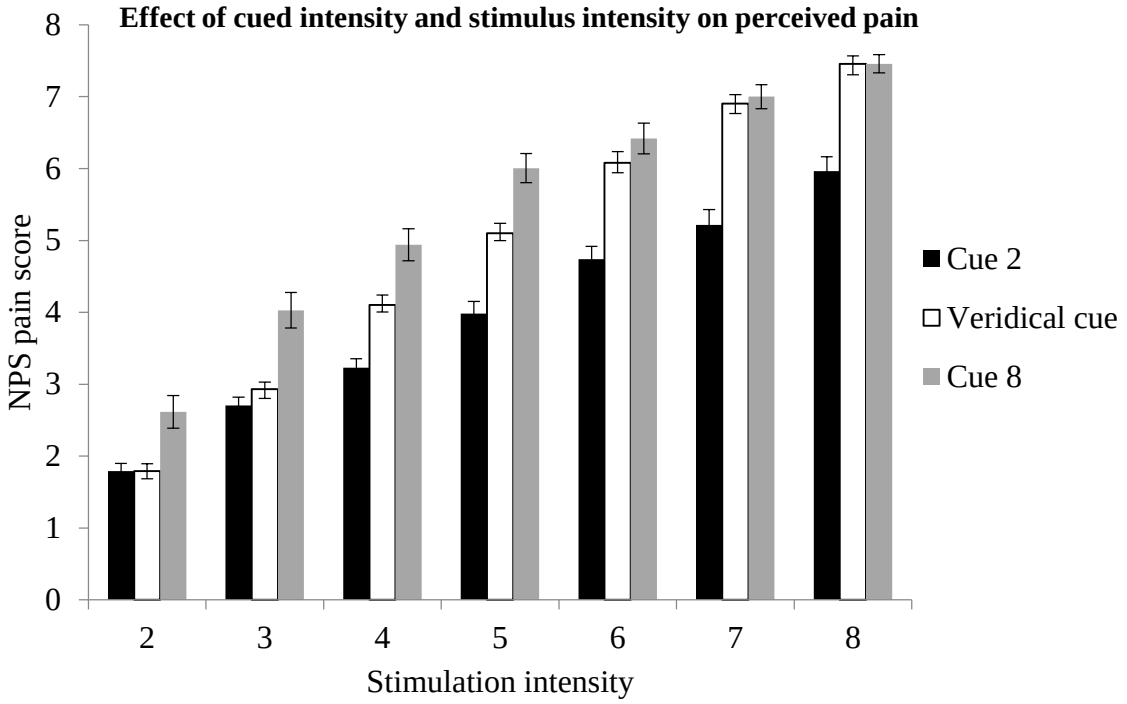

Figure 3. *Average influence of cued intensity and stimulus intensity on NPS rating, showing that a cue predicting low intensity pain (Cue 2) decreases the perceived intensity of a painful stimulus compared to baseline (veridical cue), and a cue predicting high intensity pain (Cue 8) increases the perceived intensity compared to baseline. Error bars represent the standard error of the mean.*

The results from fitting the basic model indicate that all the terms are significant, suggesting that the cubic polynomial in PE fits the data well (table 2). The coefficients, particularly for the PE^2 and PE^3 terms, are small in magnitude, which is expected as some of the values attained by PE^2 and PE^3 are rather large (e.g. at the boundary $PE^3 = 6^3$) and the model aims to model the average PE_{sub} over the PE range.

Table 2: *Results of the basic models fitted in Dataset 1 and 2*

Polynomial mixed model: PE_{sub}						
	Dataset 1			***Dataset 2***		
Predictor	***Estimate***	***SE***	***P-value****	***Estimate***	***SE***	***P-value****
Intercept	-.13	.04	.003	-.44	.05	< .0001
PE	-.33	.02	<.0001	-.27	.02	<.001
PE^2	-.01	.002	<.0001	-.01	.002	<.001
PE^3	.002	.001	.0003	.004	.001	<.0001
AIC	7794.981			7639.873		
BIC	7823.44			7668.121		
Log-likelihood	-3892.491			-3814.936		

*marginal p-values

Figure 4 shows the curves of the relationship between PE and PE_{sub}. In Dataset 1 (left plot), the curve reflects the predicted cubic relationship between PE and PE_{sub}, where as PE increases (in either negative or positive direction), PE_{sub} also increases, but at the higher levels of PE, PE_{sub} decreases. Although the shape of the curve supports our hypothesis of a 'tipping point', at high magnitude of positive PE the effect was subtle, which brought the robustness of this relationship into question. We thus collected a second, independent dataset to test whether the predicted relationship would be replicated (Dataset 2, right plot). As can be seen in this plot, the second dataset more clearly reflects the cubic relationship, suggesting the effect is robust and supporting our hypothesis of a 'tipping point' at high levels of PE.

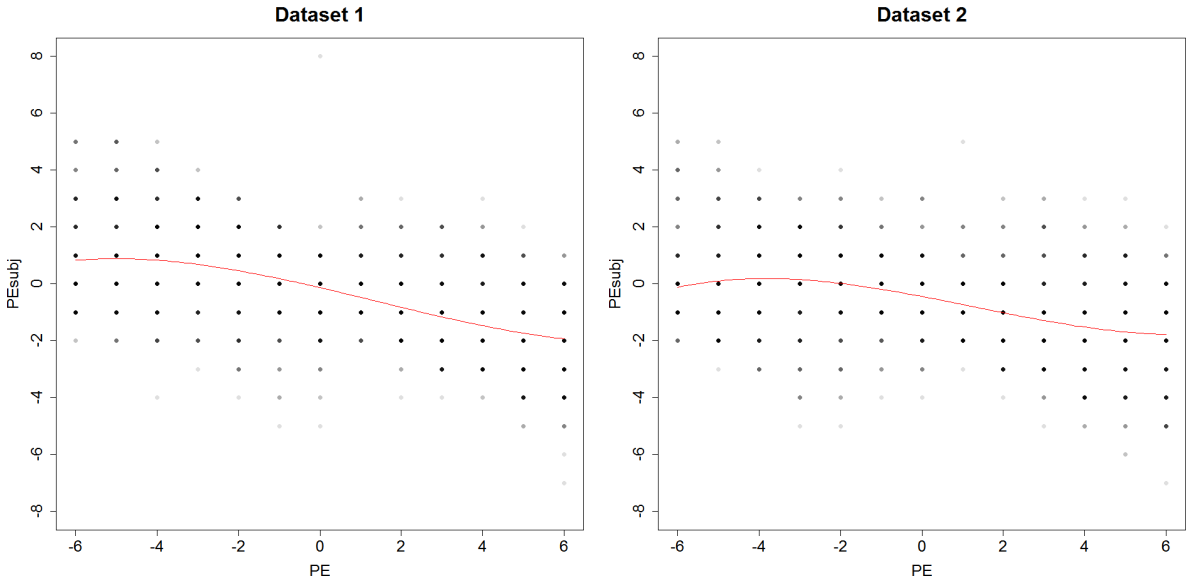

Figure 4: *Initial fitted models per dataset, both of which show a cubic relationship between PE and $PE_{sub,}$. This relationship is particularly clear in Dataset 2.*

Complex model

Preliminary analysis of the complex model indicated that the quartic term in PE should be included alongside the cubic term (Supplementary Materials). This is also supported by figure 6 (Supplementary Materials). The figure indicates that for some individuals in Dataset 1, e.g. participants 25 and 6, the relationship is described by a cubic polynomial, whereas for other individuals, such as participants 11, 14 and 28, a quartic polynomial is appropriate. Once the saturated model was selected, the models without random effects, with just random intercept, and with both random intercept and random slope were compared using the maximum likelihood test to identify which random effects were needed in the model. The results verified that both the random intercept and random slope should be included in the model (Supplementary Materials).

Table 3 summarises the results of the complex model fitted on Datasets 1 and 2. Both sets of results suggest that a quartic model in PE, with an effect for Trial and some interactions between Trial and PE are needed to describe the relationship between PE and $PE_{sub.}$ Figure 5 visualises the relationship between PE and PE_{sub} based on this model, at different levels of Trial, for Datasets 1 and 2. Figure 5 also reflects some subtle differences in the effect of Trial between the two datasets. In Dataset 2, the 'tipping point' is most pronounced at the beginning of the study session and becomes less pronounced over the course of the task. At the beginning of the study session (Trial 1) the curve's polynomial cubic shape is more pronounced and clearly supports our hypothesis about the presence of a "tipping point" in response to both positive and negative PE. As participants progress through the task to Trial 60, the curve retains its earlier shape (though less pronounced). At Trial 120 (the final Trial), the curve appears more linear, which suggests that that the relationship between PE and PE_{sub} weakened at the end of the experiment, indicating that the 'tipping point' effect decreased over the course of the task. The curve also moves closer to PE_{sub}=0, which suggests that the influence of expectation on average decreased over the task. Dataset 1 shows the same pattern of results in the negative PE condition but a slightly different effect of Trial in the positive PE condition. Here, the 'tipping point' is least pronounced at the beginning of the study session (Trial 1). Progressing to Trial 60, the curve increases, and by Trial 120, it is most pronounced.

Table 3: Results of the complex models fitted in Dataset 1 and 2

Polynomial mixed model: PE_{sub}						
	Dataset 1			***Dataset 2***		
Predictor	***Estimate***	***SE***	***P-value****	***Estimate***	***SE***	***P-value****
Intercept	.05	.14	.01	-.19	.15	<.0001
PE	-.39	.046	<.0001	-.43	.05	<.0001
Trial	-.005	.0013	<.0001	-.003	.0015	.0016
PE^2	.045	.015	<.0001	-.02	.015	<.0001
PE^3	.002	.001	<.0001	.007	.001	<.0001
PE^4	-.002	.0004	<.0001	.00007	.0004	.0326
PExTrial	.0008	.0005	<.0001	.0028	.0006	<.0001
PE^2xTrial	.0003	.0002	.11	-.0001	.0002	.17
PE^3xTrial	.00001	.00002	.61	-.00006	.00002	.0028
PE^4xTrial	.00001	.000006	.03	.000006	.000006	.30
AIC	7019.382			7018.041		
BIC	7099.065			7097.137		
Log-likelihood	-3495.691			-3495.021		

*Sequential p-values

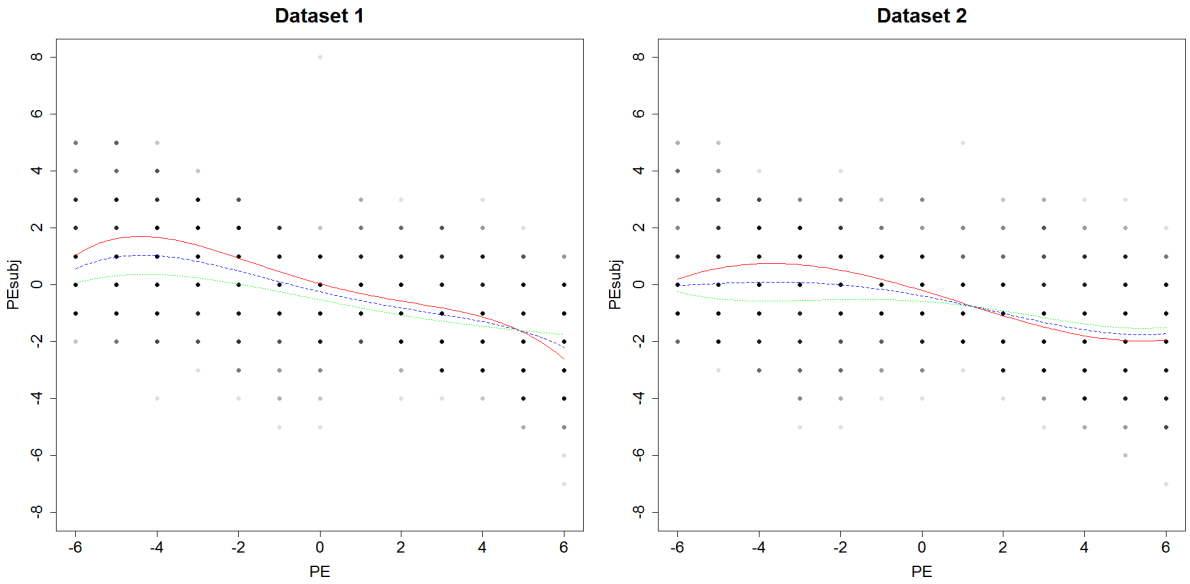

Figure 5: *Polynomial relationship between PE and PE_{sub} per dataset; Trial 1 (red solid curve), Trial 60 (blue dashed curve), Trial 120 (green dotted curve)*

Table 3 shows that the two datasets agree that the main effects as well as the interactions between PE and Trial should be included in the model, and that the interaction between PE^2 and Trial is not significant. However, there is no agreement whether the interactions between the higher order polynomial terms (PE^3 and PE^4) and Trial are significant, which suggests that the change in the effects pain expectations had on perception during the course of the experimental session was slightly different in the two studies.

It is also possible to explore how well the model captures individuals' behaviours, by plotting the smooth trajectories for each participant. In Dataset 1 (obtained using the fitted values; Figure 6, Supplementary Materials). In general, the models (black line) fit the data well. However, for some individuals in Dataset 1, such as participants 6 and 12, the smooth trajectory based on the fitted values seems to ignore the more extreme PE_{sub} values, thus producing a flatter trajectory. See figure 7 (Supplementary Materials) for these plots for Dataset 2, where a similar pattern of results is shown.

Discussion

We report an investigation into the influence of expectation (cued pain intensity), incoming sensory information (actual pain stimulus intensity) and the discrepancy between them (PE magnitude) on perceived pain. This is the first study to systematically vary pain PE magnitude and test the influence on the resulting pain perception. Results overall indicate that a non-monotonic polynomial describes the relationship between PE and $PE_{sub,}$ which suggests that when stimulus intensity was highly discrepant to cued intensity, pain intensity ratings were less influenced by the cued intensity. This supports our preregistered hypothesis that there is a 'tipping point' or a boundary to the influence of

expectations on pain perception. These results extend our understanding of the relationship between expectation and perception, because they suggest that during immediate, online perception, there is a boundary effect on expectation's influence on perception.

In order to test our hypothesis about the relationship between PE and PE_{sub}, we fitted a linear model, allowing for polynomial terms in PE to capture a 'tipping point' where PE_{sub} decreased when absolute PE increased. We first implemented a basic model testing for the hypothesised cubic relationship between PE and $PE_{sub.}$ In Dataset 1 the result of the model supported our hypothesis, but for positive PEs (where pain was higher than expected) the effect was significant but small. To further examine whether this was a true effect, we collected a second, independent Dataset 2. The basic model in Dataset 2 replicated Dataset 1, now with equally pronounced cubic relationship between both positive and negative PEs and PE_{sub}.

We also implemented a more complex model where we investigated the effect of Trial on the 'tipping point' as well as putative individual differences. This was motivated by the observation that sensitivity to painful stimulation can vary over time, and by our own result showing a negative correlation between Trial and pain intensity ratings (Bingel, Schoell, Herken, Büchel, & May, 2007; Li & McNally, 2014; McHugh, Barkus, Huber, Capitão, Lima, Lowry, & Bannerman, 2014; Vlaeyen, 2015). It was also motivated by our own and others' findings that the experience of pain is strongly affected by individual differences such as optimism, anxiety, suggestibility, and reward responsiveness (Pascalis, Chiaradia, & Carotenuto, 2002; Geers, Helfer, Kosbab, Weiland, & Landry, 2005; Scott, Stohler, Egnatuk, Wang, Koeppe, & Zubieta, 2007; Morton, Watson, El-Deredy, & Jones, 2009; Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009). This is in line with previous work showing pain expectation effects are best modelled by considering individual variation in pain expectation (Hoskin, Berzuini, Guo, & Talmi, 2018). This more complex analysis was preregistered prior to the collection of Dataset 2 (osf.io/5r6z7)**.** With this more complex model we found that the boundary effects became less important over time in all conditions other than in the positive PE condition of Dataset 1. In this condition particularly, they became more pronounced later in the task. This suggests that participants became more sensitive to high magnitude PE later in the task. The fact that this appeared only in the positive PE condition of Dataset 1 but not in Dataset 2 suggests that boundary effects when pain is higher than expected are perhaps more influenced by individual differences. For example, the trajectory of placebo responses is sensitive to individual personality traits such as dispositional optimism (Morton, Watson, El-Deredy, & Jones, 2009). It is possible that by chance there was a higher proportion of optimists, or of some other unobserved individual trait, in Dataset 1 compared to Dataset 2, which influenced the trajectory of responses to higher-than-expected pain. Our modelling approach afforded a quantification of boundary effects at the individual level, to enable future work to explore the predictive power of individual personality traits on the relationship of PE vs PE_{sub}.

There is a wealth of evidence for prediction error-driven updating of individual's internal models over time (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Seymour, O'Doherty, Dayan, Koltzenburg, Jones, Dolan, Friston, & Frackowiak, 2004; Moutoussis, Bentall, Williams, & Dayan, 2008; Mcglone, Olausson, Boyle, Jones-Gotman, Dancer, Guest, & Essick, 2012). Indeed, unexpected sensory input leads to increased neural activity which resembles a PE signal (Delgado, Li, Schiller, & Phelps, 2008; Talmi, Atkinson, & El-Deredy, 2013; McHugh, Barkus, Huber, Capitão, Lima, Lowry, & Bannerman, 2014; Geuter, Boll, Eippert, & Büchel, 2017; Hird, El-Deredy, Jones, & Talmi, 2018). It has been previously proposed that pain perception reflects the precision-weighted average of expectation and sensation (Colloca & Benedetti, 2006; Colloca, Sigaudo, & Benedetti, 2008; Yeung, Colagiuri, Lovibond, & Colloca, 2014). Here, instead of looking for changes over time, we test for a role of PE on a dynamic moment-by-moment basis. We show that prediction error modulates the weight of expectation on "online" momentary perception.

A putative pathway for the boundary effects of expectations that we observed could be the periaqueductal gray-rostral ventral medulla-spinal cord (PAG-RVM-SC). The neural expression of PE has been captured in the PAG, and the PAG-RVM-SC has been identified as a potential pathway for the influence of expectations on perception, where endogenous opioids in this pathway signal the influence of top-down expectations (Büchel, Geuter, Sprenger, & Eippert, 2014). In the context of our results, the difference between cued intensity and stimulus intensity could be calculated in the PAG. When the stimulus intensity is highly discrepant to the cued intensity and the influence of expectations is decreased, this may be expressed in altered ascending signalling of pain from the PAG (Hosobuchi, Adams, & Linchitz, 1977; Johansen, Tarpley, LeDoux, & Blair, 2010; Ritter, Franz, Dietrich, Miltner, & Weiss, 2013; Büchel, Geuter, Sprenger, & Eippert, 2014). Future studies could repeat this study using fMRI to test whether the non-monotonic relationship we observed between PE and PE_{sub} is visible in the PAG.

There are three limitations to this study. First, we induced expectations of both high and low pain. The experience of expecting high pain is affectively different to expecting a low pain. For example, expecting low pain may decrease anxiety, whereas expecting high pain may increase anxiety, and anxiety is known to influence the perceived intensity of pain which could interact with the effect of expectation (Wager, 2005). Expecting high pain could also increase attention to the stimulus intensity; attention also modulates responses to pain (Miron, Duncan, & Bushnell, 1989; Bantick et al., 2002; Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002). Future studies could repeat the study while recording anxiety and attention to pain to test whether they influence the effects of pain expectations reported here. Second, here stimulus intensity was varied to elicit different levels of PE. A higher stimulus intensity is likely to be more salient, and thus have more importance assigned to it which could increase its influence on perceived pain (Borsook, Edwards, Elman, Becerra, & Levine, 2013). It would be useful to measure the effect of pain intensity cues from low pain intensity up to high pain

intensity and all intermediates steps, whilst maintaining a constant level of stimulus intensity, to test the effect of PE on ratings and remove the variable of pain intensity. Third, predictive coding argues that the influence of expectation on perceived pain is also modulated by the certainty (the inverse variability) of the pain stimulus intensity (Brown, Seymour, Boyle, El-Deredy, & Jones, 2008; Brown, Seymour, El-Deredy, & Jones, 2008; Tabor, Thacker, Moseley, & Kording, 2017; Tabor & Burr, 2019). A potential change in certainty of the cued expectation over the course of the task could relate to the different effects of Trial observed in the positive PE condition between Dataset 1 and Dataset 2.

To conclude, we explored boundary effects of expectation in pain perception, and validated our results in two independently collected datasets, the second of which was preregistered (osf.io/5r6z7)**.** We show that when pain is very different to what was expected, perception moves closer to the pain stimulus intensity, especially when pain is much lower than expected. Pain perception is bewilderingly variable and pain is an important subjective experience which affects all individuals to varying degrees (Diatchenko, Slade, Nackley, Bhalang, Sigurdsson, Belfer, Goldman, Xu, Shabalina, Shagin, Max, Makarov, & Maixner, 2005). Chronic pain in particular is a prevalent debilitating experience with great personal and socioeconomic costs. The economic cost of chronic pain is greater than most other conditions, and it causes suffering and significantly reduces quality of life, linked to issues in mental health, sleep, physical and cognitive functioning (Phillips, 2009). Treatment for chronic pain is often ineffective and associated with undesirable side-effects (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006; Benyamin, Trescot, Datta, Buenaventura, Adlaka, Sehgal, Glaser, & Vallejo, 2008; Juurlink & Dhalla, 2012; Franklin, 2014). There is a clear need for more precise models of pain perception to inform treatment, particularly to inform non-drug interventions. Our results provide insight into the influence of the relationship between prior expectation and sensory evidence on pain perception in real time, and bring us closer to a quantitative mathematical model of pain. Furthermore, in the clinic, it is usual to give reassurance about a painful or unpleasant experience. Our results indicate that reassurance that is completely discrepant with ensuing painful or unpleasant events may not always be useful for a patient.

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Supplementary Materials

Before fitting the complex model, we carried out a preliminary analysis to assess which fixed effects to include in the model, to determine the "saturated model". After visual inspection of figure 6, we checked to check whether a quartic term in PE would also be useful in describing its relationship to PE_{sub}, as some of the participants in Dataset 1 exhibited a quartic curve. We formally tested the significance of the quartic term by comparing the cubic PE model (basic model) with a quartic PE model through a hypothesis test. The F-test confirmed that the quartic term was significant (p-value <0.01). Adding the Trial and interaction terms in both the basic and quartic polynomial models and repeating the test further verified the significance of the quartic term (p-value <0.01).

Based on the saturated model, we then continued our preliminary analysis by exploring which random effects we needed to include in the model. Figure 6 suggested that perhaps both a random intercept and random slope in PE would be necessary. This is because both the intercept and the linearity for each curve seem to vary across participants; compare for example participants 13 and 17. A likelihood ratio test was used to compare the saturated models without any random effects, with just random intercept and with both a random intercept and random slope, and the results confirmed that the latter model was the best (p-value <0.01).

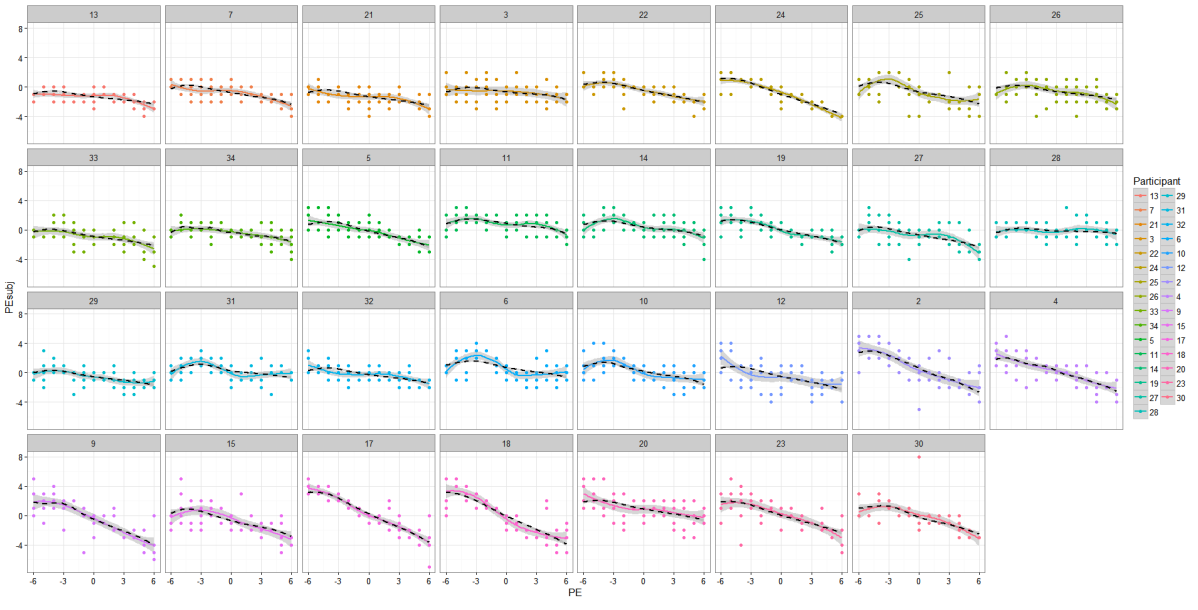


Figure 6: *Smooth trajectories illustrating the relationship between PE and PE_{sub} for each subject in Dataset 1, based on the fitted values (black dashed) and based on the data (solid curves)*

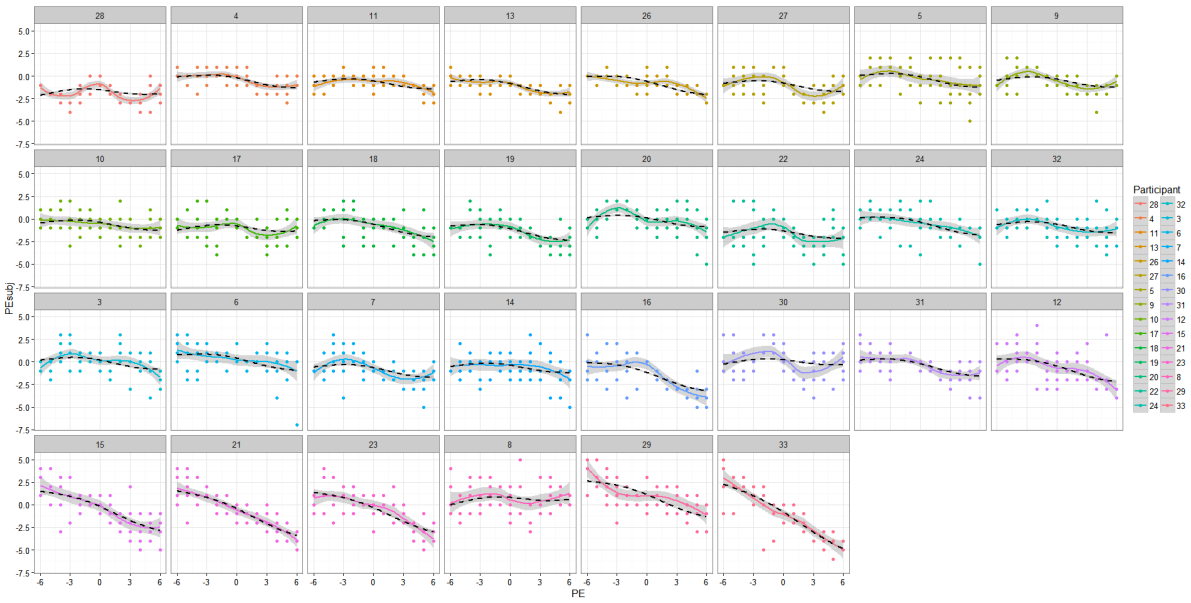
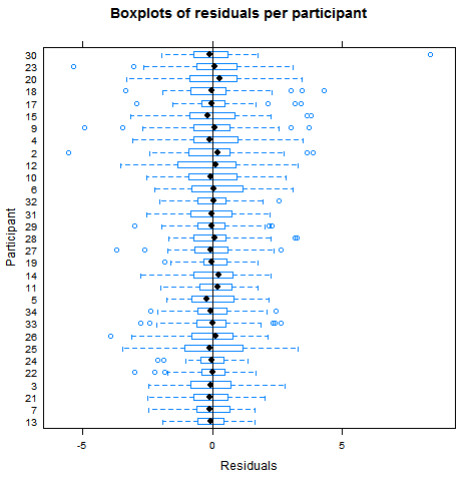
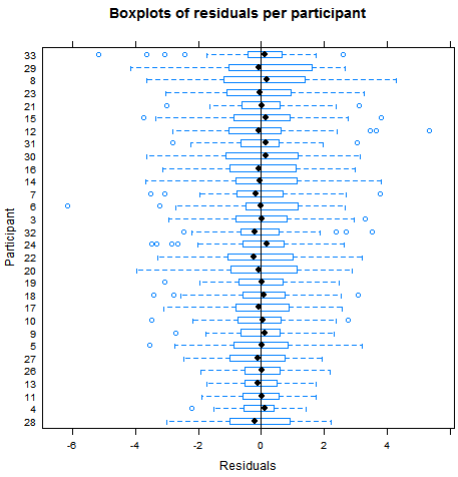


Figure 7: *Smooth trajectories illustrating the relationship between PE and* PE_{sub} *for each subject in dataset 2, based on the fitted values (black dashed) and based on the data (solid curves)*





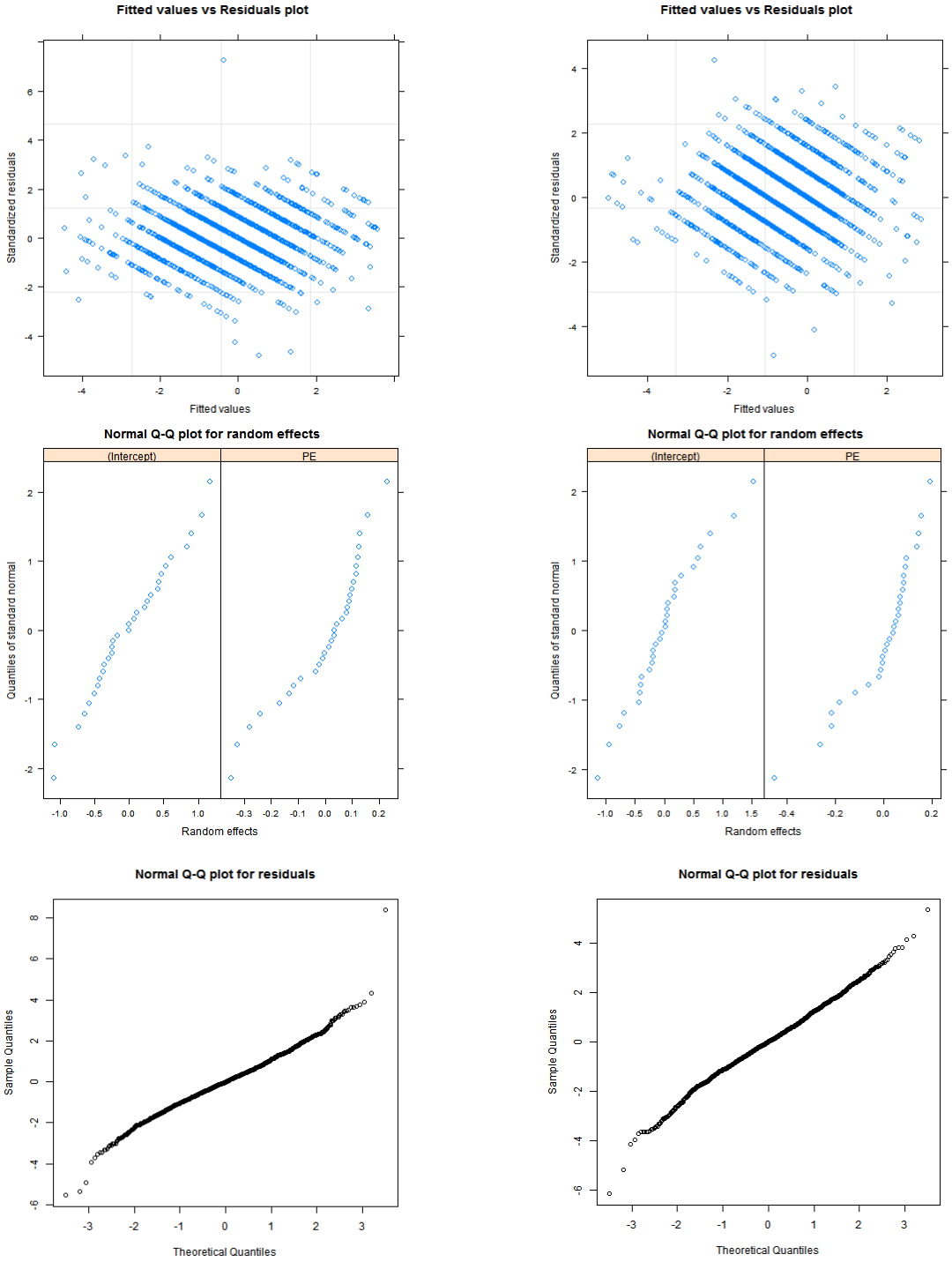


Figure 8: *Diagnostic plots for the quartic polynomial model for Dataset 1 (left column) and Dataset 2 (right column). The boxplots show the residuals are centered around 0; the plot of fitted values vs residuals shows the residuals are spread around 0 evenly (no distinguishing pattern); the qq-plots show that the Normality assumption for both random effects and residuals is reasonable.*

The results of the complex model (table 3) show that the estimates of PE, PE^3 and Trial are similar across datasets in terms of their sign and magnitude. This is important because these estimates reflect two key features of the relationship between PE and $PE_{sub,}$. First, at the beginning of the study (i.e. when Trial number is small), the effect of the polynomial terms dominates that of the interaction

terms (because the size of the main effects coefficients is larger). Therefore, the negative sign (and size) of the linear PE term and the positive sign (and size) of the cubic PE term, ensure the tipping point for negative PE appears where it should be (as hypothesised in figure 1). Second, as Trial number increases, the negative sign of the Trial term indicates that the value attained by PE_{sub} corresponding to $PE = 0$ shifts downwards over the course of the task. The size of the Trial term also determines how fast this shift occurs as Trial number increases. This is better visualised in Figure 3 which shows that for Trial 120 (green curve), the point at which the curve intersects the PE_{sub} axis is lower compared to Trial 1 (red curve) or Trial 60 (blue curve).

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