Temporal–spectral signaling of sensory information and expectations in the cerebral processing of pain

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The perception of pain is shaped by somatosensory information about threat. However, pain is also influenced by an individual’s expectations. Such expectations can result in clinically relevant modulations and abnormalities of pain. In the brain, sensory information, expectations (predictions), and discrepancies thereof (prediction errors) are signaled by an extended network of brain areas which generate evoked potentials and oscillatory responses at different latencies and frequencies. However, a comprehensive picture of how evoked and oscillatory brain responses signal sensory information, predictions, and prediction errors in the processing of pain is lacking so far. Here, we therefore applied brief painful stimuli to 48 healthy human participants and independently modulated sensory information (stimulus intensity) and expectations of pain intensity while measuring brain activity using electroencephalography (EEG). Pain ratings confirmed that pain intensity was shaped by both sensory information and expectations. In contrast, Bayesian analyses revealed that stimulus-induced EEG responses at different latencies (the N1, N2, and P2 components) and frequencies (alpha, beta, and gamma oscillations) were shaped by sensory information but not by expectations. Expectations, however, shaped alpha and beta oscillations before the painful stimuli. These findings indicate that commonly analyzed EEG responses to painful stimuli are more involved in signaling sensory information than in signaling expectations or mismatches of sensory information and expectations. Moreover, they indicate that the effects of expectations on pain are served by brain mechanisms which differ from those conveying effects of sensory information on pain.

Pain is not only shaped by sensory information but also by an individual’s expectations. Here, we investigated how commonly analyzed electroencephalography (EEG) responses to pain signal sensory information, expectations, and discrepancies thereof (prediction errors) in the processing of pain. Bayesian analysis confirmed that pain perception was shaped by objective sensory information and expectations. In contrast, EEG responses at different latencies (including the N1, N2, and P2 components) and frequencies (including alpha, beta, and gamma oscillations) were shaped by sensory information but not by expectations. Thus, EEG responses to pain are more involved in signaling sensory information than in signaling expectations or prediction errors. Expectation effects are obviously mediated by other brain mechanisms than the effects of sensory information on pain.

Significance

Pain is not only shaped by sensory information but also by an individual’s expectations. Here, we investigated how commonly analyzed electroencephalography (EEG) responses to pain signal sensory information, expectations, and discrepancies thereof (prediction errors) in the processing of pain. Bayesian analysis confirmed that pain perception was shaped by objective sensory information and expectations. In contrast, EEG responses at different latencies (including the N1, N2, and P2 components) and frequencies (including alpha, beta, and gamma oscillations) were shaped by sensory information but not by expectations. Thus, EEG responses to pain are more involved in signaling sensory information than in signaling expectations or prediction errors. Expectation effects are obviously mediated by other brain mechanisms than the effects of sensory information on pain.
Considering the preeminent role of the integration of sensory information and expectations in the processing of pain, an application of predictive coding frameworks to pain is obvious (15, 43–46). This is even more appealing as abnormally precise predictions and/or abnormal updating of predictions might figure prominently in the pathophysiology of chronic pain (47–49). Consequently, recent functional magnetic resonance imaging (fMRI) studies have applied predictive coding frameworks to the processing of pain (50, 51). The results revealed a spatial dissociation of the encoding of stimulus intensity, predictions, and PEs in the processing of pain. Most recently, a first EEG study applied a predictive coding framework to oscillatory responses to noxious stimuli (52). The findings indicated that alpha-to-beta and gamma oscillations signal expectations and PEs in the processing of pain, respectively. However, a model which comprehensively describes how evoked potentials at different latencies—which are the electrophysiological gold standard for assessing the cerebral processing of pain—and oscillations at different frequencies signal sensory information, expectations, and PEs in the processing of pain is lacking so far.

To systematically investigate whether and how evoked and oscillatory EEG responses to painful stimuli signal stimulus intensity, expectations, and PEs, we applied brief painful stimuli to healthy human participants and independently modulated sensory information and expectations. We hypothesized that alpha/beta and gamma oscillations signal predictions and PEs, respectively. We further expected that already the earliest evoked responses to noxious stimuli are shaped by predictions, whereas later responses are also shaped by PEs. To test these hypotheses, we performed Bayesian ANOVAs and model comparisons on pain ratings and EEG responses. Pain ratings confirmed that pain intensity was shaped by both sensory information and expectations. In contrast, EEG responses at different latencies (N1, N2, and P2 components) and frequencies (alpha, beta, and gamma oscillations) were shaped by sensory information but not by expectations. Together, these findings reveal that commonly analyzed EEG responses to painful stimuli are more sensitive to sensory information than to expectations or PEs. Moreover, they indicate that expectations effects on pain are served by other brain mechanisms than sensory effects on pain.

**Results**

To investigate how EEG responses to brief painful stimuli signal stimulus intensity, expectations, and PEs in the processing of pain, we employed a probabilistic cueing paradigm in 48 healthy human participants. We applied brief painful heat stimuli to the left hand and independently modulated stimulus intensity and expectations in a 2 × 2 factorial design. To modulate stimulus intensity, we applied painful stimuli of two different levels (high intensity [hi] and low intensity [li]). To modulate expectations, the painful stimuli were preceded by one out of two visual cues. The high-intensity (HE) cue was followed by a high stimulus in 75% of the trials and by a low stimulus in 25% of the trials. Vice versa, the low-intensity (LE) cue was followed by a low stimulus in 25% of the trials and by a high stimulus in 75% of the trials. The experiment thus comprised four trial types (Fig. 1A): high intensity, high expectation (hiHE); high intensity, low expectation (hiLE); low intensity, high expectation (liHE); and low intensity, low expectation (liLE). In each trial, the participants were asked to provide a rating of the perceived pain intensity on a numerical rating scale ranging from 0 (no pain) to 100 (maximum tolerable pain). In addition, skin conductance responses (SCRs) were recorded. Fig. 1B shows the sequence of a single trial.

During the experiment, we recorded EEG and assessed the most consistently observed EEG responses to painful stimuli (12). Evoked EEG responses included the N1, N2, and P2 components. Oscillatory responses included stimulus-induced changes of alpha, beta, and gamma oscillations. In addition, we quantified brain activity before the painful stimulus, including the stimulus preceding negativity [SPN (29)] and oscillatory activity at alpha and beta frequencies.

Building upon previous investigations (50, 53), we made specific predictions how EEG responses signaling stimulus intensity, expectations, PEs, or combinations thereof are modulated across the four trial types (Fig. 2).

To formally test these predictions, we pursued two complementary approaches (50, 53). First, we performed repeated measures ANOVAs (rmANOVA) with the independent variables stimulus intensity and expectation. In these rmANOVAs, responses signaling stimulus intensity and expectations would manifest as main effects, whereas responses signaling PEs would manifest as interactions. To quantify effects and to facilitate interpretation of negative findings, we primarily performed Bayesian rmANOVA (54). In Bayesian rmANOVAs, the Bayes factor (BF) is the ratio between the likelihood of the data given the effect of interest and the likelihood of the data without the effect of interest. BF > 3 and BF > 10 indicate moderate and strong evidence in favor of the effect of interest, whereas BF < 0.33 and BF < 0.1 indicate moderate and strong evidence against the effect of interest, respectively (54). Complementing Bayesian inference, we also performed traditional frequentist rmANOVA.

Detailed results of both Bayesian and frequentist rmANOVAs are provided in SI Appendix, Tables S1–S3. Second, we employed Bayesian model comparisons based on single-trial data to formally test which combination of stimulus intensity, expectations, and PEs best explained the observed EEG responses. Building upon previous studies (50, 53), we specifically compared models where stimulus intensity only (INT model), stimulus intensity and expectations (INT+EXP), and...
The Effects of Stimulus Intensity, Expectations, and PEs on EEG Responses to Noxious Stimuli. To investigate the effects of stimulus intensity, expectations, and PEs on EEG responses, we calculated rmANOVAs as done for pain intensity ratings and SCR. Bayesian rmANOVA showed strong evidence for a main effect of stimulus intensity on all EEG responses (BF > 1.2 × 10^4). N1, N2, and P2 responses (Fig. 4 and SI Appendix, Table S2) as well as poststimulus gamma oscillations and alpha and beta suppressions (Fig. 5 and SI Appendix, Table S3) were stronger in the hi than in the li conditions. Further analyses with baseline correction of EEG responses yielded similar results (SI Appendix, Table S4).

In contrast, we found moderate evidence against an expectation effect on all EEG responses (all BF < 0.22) apart from the N1, where evidence was inconclusive (BF = 0.39). In addition, we found moderate evidence against an interaction of stimulus intensity and expectation for all EEG responses (all BF < 0.26). We, thus, observed that the most consistently observed evoked and oscillatory EEG responses to noxious stimuli were shaped by stimulus intensity but not by expectations or PEs.

To test for effects on brain activity other than the predefined EEG responses, ANOVAs and cluster-based permutation tests were performed across the poststimulus time period from 0 to 1 s, all frequencies, and all channels which corroborated the results at alpha, beta, and gamma frequencies (SI Appendix, Fig. S3). Accordingly, model comparisons for N1, N2, and P2, alpha, beta, and gamma responses yielded stronger evidence for the INT model than for the INT+EXP (BF < 0.10) and EXP+PE (BF < 0.012) models, except for the N1, which showed inconclusive evidence regarding the comparison of the INT and the INT+EXP models (BF = 0.84). Thus, poststimulus EEG responses were consistently modulated by stimulus intensity but not by expectations.

Having found no expectation effects on EEG responses, we further asked whether the expectation effect on pain ratings expectations and PE (EXP+PE) shaped the respective responses. In line with a previous study (50), the PE was defined as aversive PE, meaning that a PE occurs only if the stimulus is more painful than expected. This model has been shown to outperform models with absolute and signed PE formulations (50) (see SI Appendix, Fig. S2 for Bayesian model comparisons using absolute and signed PE formulations).

The Effects of Stimulus Intensity, Expectations, and PEs on Pain Ratings and SCR. Before analyzing EEG responses, we investigated the effects of stimulus intensity, expectations, and PEs on pain intensity ratings. We therefore calculated rmANOVAs with the independent variables stimulus intensity and expectation. Results are shown in Fig. 3 and SI Appendix, Table S1. BFs indicated strong evidence for main effects of stimulus intensity (BF = 1.6 × 10^26) and expectations (BF = 1.2 × 10^9). Specifically, pain intensity was higher for hi than for li stimuli and higher for HE than for LE trials. Bayesian rmANOVA showed weak evidence against an interaction of stimulus intensity and expectation (BF = 0.36). To further investigate the relationship between stimulus intensity, expectations, PEs, and pain ratings, we tested INT, INT+EXP, and EXP+PE models against each other. The comparisons showed strong evidence that the INT+EXP model explained the data better than the INT (BF = 7.8 × 10^26) or the EXP+PE (BF = 2.8 × 10^-45) model. Thus, we found that stimulus intensity and expectations, but not PEs shaped pain ratings.

We next investigated how stimulus intensity, expectations and PEs shaped SCR. The rmANOVA for the SCR showed strong evidence for a main effect of stimulus intensity (BF = 3.2 × 10^13), i.e., the amplitude of SCRs was higher in hi than in li trials (SI Appendix, Fig. S1 and Table S1). However, we found inconclusive evidence regarding a main effect of expectation (BF = 0.68) and weak evidence against an interaction of stimulus intensity and expectation (BF = 0.24) on SCR. Bayesian model comparisons of single-trial SCRs showed evidence that the INT model explained the SCR just as well as the INT+EXP model (BF = 1.0) and better than the EXP+PE (BF = 1.4 × 10^-6) model (Fig. 3).

Taken together, we found strong effects of stimulus intensity on pain intensity ratings and SCRs. Moreover, we found a strong effect of expectations on pain intensity but only inconclusive evidence for an effect of expectations on SCRs. Furthermore, we did not observe an interaction between stimulus intensity and expectation in shaping pain ratings and SCRs.

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![Fig. 2. Predicted response patterns for responses signaling stimulus intensity (INT model), expectations (EXP model), prediction errors (PE model), or combinations thereof (INT+EXP model, EXP+PE model).](Image 330x282 to 335x320)

![Fig. 3. Effects of stimulus intensity, expectations, and PEs on pain ratings and SCR. (A) Raincloud plots (S5) of pain ratings and SCRs in hiLE, hiHE, liLE, and liHE conditions. The dotted lines show the probability density function of the individual means, indicated by dots. Boxplots depict the sample median as well as first (Q1) and third quartiles (Q3). Whiskers extend from Q1 to the smallest value within Q1 – 1.5 × interquartile range (IQR) and from Q3 to the largest values within Q3 + 1.5 × IQR. (B) Bayesian model comparisons between stimulus intensity (INT) and stimulus intensity + expectations (INT+EXP) models, stimulus intensity (INT) and expectations + PE (EXP+PE) models, and stimulus intensity + expectations (INT+EXP) and expectations + PE (EXP+PE) models. The bars depict the natural logarithm of the BFs. The discontinuous bars indicate log(BF) > 20 or log(BF) < −20. The dotted lines indicate the bounds of strong evidence (log(BF = 0.1) and log(BF = 10)) (S4).](Image 446x285 to 452x319)
can be explained by a pattern of the different EEG responses rather than each response in isolation. We therefore performed a multiple regression analysis to test whether difference values (HE − LE) of N1, N2, P2, and alpha, beta, and gamma responses together capture the expectation effect on pain ratings. However, the multiple regression model did not explain a significant amount of variance in the data ($F_{(6, 44)} = 0.66; P = 0.68; R^2 = 0.094$).

In summary, results from rmANOVAs and model comparisons convergingly showed that stimulus intensity shapes all EEG responses. In contrast, we found evidence against an effect of expectations or mismatches of sensory information over stimuli are more involved in signaling sensory information than stimuli are more involved in signaling sensory information. Expectations, in contrast, modulated the perception of pain but not associated EEG responses. Indeed, we observed lack of expectation effects on EEG responses can indeed be interpreted as an absence of effects. These findings indicate that commonly analyzed EEG responses to painful stimuli are more involved in signaling sensory information than in signaling expectations or mismatches of sensory information.
Figure 5. Effects of stimulus intensity, expectations, and PEs on oscillatory EEG responses to noxious stimuli. (A) Grand averages of time-frequency representations (TFRs) are depicted as relative change to the baseline preceding the cue presentation (−3.3 to −2 s). For visualization, TFRs at Cz are presented. Statistical analysis was performed on absolute power values without baseline correction averaged across ROIs as indicated by the dotted boxes and marked electrodes. Topographies display the average of ROIs across all four conditions. (B) Raincloud plots (55) of alpha, beta, and gamma power in hiLE, hiHE, liLE, and liHE conditions. The clouds display the probability density function of the individual means indicated by dots. Boxplots depict the interquartile range (IQR). (C) Bayesian model comparisons between stimulus intensity (INT) and stimulus intensity + expectations (INT+EXP) models, stimulus intensity (INT) and expectations + PE (EXP+PE) models, and stimulus intensity + expectations (INT+EXP), and expectations + PE (EXP+PE) models. The bars depict the natural logarithm of the BFs. The discontinuous bars indicate log(BF) > 20 or log(BF) < −20. Dotted lines indicate the bounds of strong evidence (log(BF = 0.1) and log(BF = 10)) (54).

Expectation on pain are served by different brain mechanisms than those conveying effects of sensory information on pain and are not well captured by commonly analyzed EEG responses to noxious stimuli. We will discuss the implications of these findings for understanding the functional significance of EEG responses to pain, particularly in the context of predictive coding frameworks of brain function, and for understanding how the brain mediates expectation effects on pain.

The Functional Significance of Pain-Associated EEG Responses. Our observation that stimulus intensity shapes EEG responses to noxious stimuli is in accordance with previous studies which nearly uniformly showed such effects. Expectation effects, on the other hand, were limited to pain ratings and not found for EEG responses in the present study. At first glance, this contrasts with previous studies, which have shown that expectations significantly modulate EEG responses (20–27). However, expectation effects in those studies were weaker and less consistent than stimulus intensity effects. Moreover, limited statistical power (56) and publication bias (57) might have resulted in an overestimation of expectation effects across the literature. Thus although expectations can, in principle, shape EEG responses, the present findings indicate that these responses are more sensitive to stimulus intensity effects than to expectations. Whether this fundamental difference generalizes from expectations to other contextual modulations of pain remains to be determined. Moreover, whether these observations are specific for EEG responses to pain or generalize to EEG responses to sensory events from other modalities remains unclear.

Pain-Associated EEG Responses in a Predictive Coding Model of Brain Function. As the interaction of sensory evidence and predictions crucially shapes the perception of pain, predictive coding frameworks of brain function have been increasingly applied to the processing of pain (15, 43–46). Based on these...
considerations, recent functional imaging studies have started to investigate how the brain encodes sensory information, predictions, and PEs in the processing of pain (50, 51). The results have revealed a spatial dissociation between brain areas encoding stimulus intensity, predictions, and PEs. More precisely, a dissociation was found in the insular cortex where posterior parts signaled sensory information, whereas anterior parts additionally signaled predictions and PEs. The present study was inspired by these investigations and adapted their paradigm for EEG. We particularly aimed to assess how evoked and oscillatory brain responses at different latencies and frequencies encode sensory information, expectations, and PEs. Based on previous anatomical and physiological evidence (35, 36, 41, 42), we specifically hypothesized that alpha/beta and gamma oscillations signal predictions and PEs, respectively. We further expected that already the earliest laser-evoked responses are shaped by predictions (37, 38), whereas later responses are also shaped by PEs (39).

Our observed prestimulus effects support the idea that alpha/beta oscillations are indeed involved in signaling predictions also in the context of pain. However, Bayesian hypothesis testing of poststimulus effects provided evidence against the hypothesis that predictions and PEs shape evoked and oscillatory responses to noxious stimuli. This contrasts with the results of a recent EEG study (52), which showed that poststimulus alpha/beta oscillations and gamma oscillations were shaped by predictions and PEs, respectively. This difference between the previous and the present study might be due to different durations of the employed noxious stimulation models. The previous study used contact-heat stimuli of a few-seconds duration, whereas the present study used radiant-heat laser stimuli of a few-milliseconds duration. Laser stimuli are a standard tool for research on the brain mechanisms of pain and for the clinical assessment of nociceptive pathways (58). They yield a highly synchronized activation of nociceptive afferents, resulting in a short and clear-cut pain sensation. These stimuli therefore offer
the opportunity to not only detect non–phase-locked oscillatory responses but to also to record phase-locked evoked oscillations and to determine their role in signaling sensory information, expectations, and PEs as previously done in other modalities (59, 60). However, predictive coding concepts propose that the precision of sensory information and predictions crucially determines their weight in further processing (43). Thus the brief laser stimuli of the present study might yield sensory information with a high precision and weight, which in turn might result in a relative down weighting of predictions. Hence, for very brief and clear-cut stimuli, the influence of sensory information might outweigh the influence of predictions and PEs on EEG responses.

In the present study, we performed direct Bayesian model comparisons to assess the role of EEG responses in the signaling of sensory evidence, expectations, and PEs in the processing of pain. While our results reveal that evoked and oscillatory EEG responses—which are commonly used to assess brain processes related to pain for research and clinical practice—are more involved in signaling sensory evidence than expectations or PEs, it is important to note that these findings do neither argue in favor of nor against predictive coding models of brain function. Our findings should thus not discourage the application of predictive coding frameworks to the processing of pain but rather encourage the search for brain features—other than the commonly analyzed EEG responses—that signal predictions and PEs in the processing of pain. Such future approaches might build upon recent predictive coding models for nociceptive processing in animals (61) and for the perception of stimuli from other modalities in humans (40).

Brain Mechanisms of Expectation Effects on Pain. Our observation of expectation effects on the perception of painful stimuli without effects on associated EEG responses supports that neither evoked nor oscillatory EEG responses to noxious stimuli represent a reliable correlate of pain (62). This dissociation might also be relevant for the search for brain-based biomarkers of pain (63). Instead, our findings indicate that EEG responses rather represent a correlate of sensory processing, which is not always sensitive to contextual modulations. Thus, other processes not captured by commonly analyzed EEG responses to noxious stimuli likely contribute to contextual modulations of pain. These processes might include cognitive evaluation, pain affect, decision making, and reward processing. Such higher-level processes might be less strictly time locked to noxious stimuli and might therefore not be captured by commonly analyzed EEG responses. Furthermore, these processes might take place in deeper brain areas such as the striatum, medial temporal lobe areas, and the brainstem, which are involved in expectation effects on pain (64–67) but are not well captured by EEG. Moreover, expectation effects might not manifest in evoked potentials and/or oscillatory responses on the sensor level, as these are a mixture of neural responses from different brain areas but might only manifest in certain brain areas. Thus source space analyses—which can help to disentangle mixtures of neural responses from different brain areas—might be more sensitive to expectation effects than sensor space analysis. Moreover, such source space analyses also allow for analyzing connectivity between sources. Considering the high complexity of the pain experience and its cerebral substrates, such connectivity analyses are particularly promising. However, source space analyses of EEG signals are inherently ambiguous, and common EEG approaches to the cerebral processing of pain therefore rely on sensor space as done in the current study.

In this way, the current EEG findings complement fMRI studies showing that the influence of contextual factors including expectations and placebo effects on pain are mediated by spatial patterns other than those capturing sensory processing (68–70). This is also in accordance with previous fMRI studies on predictive coding in the processing of pain, which showed that the nociceptive sensitive neurologic pain signature was mostly shaped by stimulus intensity rather than expectations (50, 51). Moreover, expectation effects on pain are likely not homogenous. For instance, it has been shown that expectation effects induced by social information and associated learning (71) as well as positive and negative expectation effects (66) differ fundamentally.

Conclusions. The present results indicate that commonly analyzed EEG responses to noxious stimuli are more sensitive to sensory processes than to expectations or mismatches between sensory processes and expectations. This finding provides insights into the functional significance of the complex spatial–temporal–spectral patterns of brain activity associated with pain. Moreover, our observations might motivate and guide further investigations on how the brain signals sensory information, predictions, and PEs in the processing of pain. Understanding these processes might also have implications for understanding the brain mechanisms of chronic pain, which have been related to abnormally precise predictions (47–49).

Materials and Methods
Participants. This study was performed in healthy human participants who were recruited through advertisements on an online platform of the Technical University of Munich. Prior to any experimental procedures, all participants gave written informed consent. The study protocol was approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich and preregistered at ClinicalTrials.gov (NCT04296968). The study was conducted in accordance with the latest version of the Declaration of Helsinki and followed recent guidelines for the analysis and sharing of EEG data (72).

Inclusion criteria were age above 18 y and right-handedness. Exclusion criteria were pregnancy, neurological or psychiatric diseases, severe internal diseases including diabetes, skin diseases, current or recurrent pain, regular intake of medication (aside from contraception and thyroid medication), previous surgeries at the head or spine, metal or electronic implants, and any previous side effects associated with thermal stimulation. A priori sample size calculations using G*Power (73) determined a sample size of 36 participants for a rmANOVA design with one group and four measurements (see Procedure for conditions), a power of 0.95, an alpha of 0.05, and medium effect sizes of f = 0.25. This corresponds to an r² (proportion variance explained) of 0.06 (74). Overall, 58 healthy human participants (29 females, age: 24.0 ± 4.3 y [mean ± SD]) were recruited. Nine participants were excluded due to either the absence of pain or low pain ratings [<10 on a numerical rating scale from 0 (no pain) to 100 (maximum tolerable pain)] during the familiarization run (n = 8), excessive startle responses in response to painful heat stimulation during the training run (n = 1), or technical issues with the response box used during catch trials (n = 1). The final sample comprised 48 participants (all right-handed, 23 females, age: 23.7 ± 3.4 y). Average clinical anxiety and depression scores obtained using the Hospital Anxiety and Depression Scale (75) were below clinically relevant cutoff scores of 8/21 (76) (anxiety: 3.0 ± 2.1; depression: 0.9 ± 1.1).

Procedure. To investigate how noxious stimulus intensity, expectations, and PEs relate to the cerebral processing of a painful stimulus and the preceding brain activity, the experiment incorporated two noxious heat stimulus intensities (hi and li) and two visual cues (HE and LE) resulting in four experimental conditions. HE cues were followed by hi stimuli in 75% of trials (hiHE) and li stimuli in 25% of trials (hiLE). Conversely, LE cues were followed by li stimuli in 75% of trials (iile) and hi stimuli in 25% of trials (hiLE; Fig. 1). The sequence of events for each trial is depicted in Fig. 1B. After a fixation period with a duration of 1.5 to 3 s, a visual cue (blue dot or yellow square) was presented for 1 s. At 1.5 s after the offset of the cue presentation, a brief painful heat stimulus was applied. At 3 s after the noxious stimulus, participants were prompted to rate the perceived pain intensity of the preceding painful heat stimulus on a numerical rating scale ranging from 0 (no pain) to 100 (maximum tolerable pain); a rating of 1 on this scale thus already indicates a minimally painful percept. To ensure sustained attention to the visual cues, a catch-to-sample task was incorporated in 10% of the trials. In these catch trials, HE and LE cues were shown simultaneously after the pain rating and participants were asked to identify the cue of the current trial by a button press.
Data were recorded using the GSR-MR module with constant voltage of 0.5 V with respect to the laser stimulus. Identical epochs as for the EEG analyses were (range: 14 to 20) trials for hiHE and hiLE conditions, respectively, and 15.2 ± 0.1% during the match-to-sample task. Prior to the main experiment, we applied a sequence of 10 heat stimuli with different intensities to familiarize the participants with the painful stimulation and the intensity rating procedure. Furthermore, participants were explicitly informed about the contingencies between cues and stimulus intensities and participated in a training run with 16 trials using the same experimental setup and contingencies as in the main experiment. The information and the training run were designed to ascertain that all participants were aware of the contingencies and to minimize learning during the main experiment. During the experiment, participants were seated in a comfortable chair and wore protective goggles and headphones playing white noise to cancel ambient sounds.

Stimulation. Painful stimuli were applied to the dorsum of the left hand using a neodymium ytrrium aluminum periokese laser (Nd:YAP; Stimul 1340, DEKA M.E.L.A. srl) with a wavelength of 1,340 nm, a pulse duration of 4 ms, and a spot diameter of ~7 mm (19). Stimulus intensity was set to 3.5 J for hi stimuli and 3 J for li stimuli (19). To avoid tissue damage and habituation/sensitization, the stimulation site was slightly changed after each stimulus.

Recordings and Preprocessing. EEG data were recorded using actiCAP snap/with 64 active sensors (Easycap) placed according to the extended 10-20 resolution) and band-pass filtering at 1 Hz using a fourth-order Butterworth filter (fourth-order Basswourt) and a 50-Hz notch filter removing line noise were applied. EEG data of all runs were concatenated. IC analysis based on the extended infomax algorithm was applied to the filtered EEG data ranging from ~4.2 to 3.2 s with respect to the laser stimulus onset and resulted in 64 ICs. ICs representing eye movements and muscle artifacts were identified (77). Subsequently, the identified ICs were subtracted from the unfiltered EEG, and data segments of 400 ms centered around data samples with amplitudes exceeding ±100 μV and data jumps exceeding 30 μV were automatically marked for rejection. Remaining artifacts were identified by visual inspection and manually marked for data jumps. Incorrectly marked segments were reexamined and corrected to the average amplitude. Finally, data were exported to Matlab (version R2019b, Mathworks), and further analyses were performed using FieldTrip [version 20200128 (78)]. We segmented the EEG data into 7-s epochs ranging from ~4 to 3 s with respect to the laser stimulus onset. All epochs including marked artifacts or trials in which the laser stimulus was not perceived as painful (pain rating = 0) were excluded from further analysis. To match the number of trials between both hi and both li conditions, respectively, the condition with the lowest trial count was identified for each participant, and the same number of trials was randomly drawn from the other conditions (maximum number = 20 trials). Further analyses were based on 17.7 ± 1.6 (range: 14 to 20) trials for hiHi/HiLE conditions and 15.3 ± 4.4 (range: 4 to 20) trials for liHi/LE conditions for each participant.

Skin conductance data were recorded using two Ag/AgCl electrodes attached to the palmar distal phalanges of the left index and middle finger. Data were recorded using the GSR-MR module with constant voltage of 0.5 V and a BrainAmp ExG MR amplifier (Brain Products) with low-pass filtering at 250 Hz and a sampling frequency of 1,000 Hz. Subsequent offline analysis included low-pass filtering at 1 Hz using a fourth-order Butterworth filter, downsampling to 500 Hz, and a visual artifact inspection. Finally, data were exported and segmented into 14-s epochs ranging from ~4 to 10 s with respect to the laser stimulus. Identical epochs as for the EEG analyses were selected. Furthermore, we had to exclude additional epochs of skin conductance data comprising marked artifacts. As a result, further analyses of skin conductance data were based on 17.7 ± 1.8 (range: 14 to 20) and 17.6 ± 1.6 (range: 14 to 20) trials for hiHe and hiLE conditions, respectively, and 15.2 ± 4.7 (range: 4 to 20) and 15.2 ± 4.8 (range: 4 to 20) trials for hiHE and liLE conditions, respectively.

Time-Domain Analysis of EEG Data. To quantify the amplitudes of laser-evoked N1, N2, and P2 responses, EEG data were band-pass filtered between 1 and 30 Hz (fourth-order Butterworth), and a baseline correction was applied using the time interval between ~3.3 and ~2.8 s before the painful stimulus. The selected baseline interval preceded the visual cue to avoid expectation effects during the low-stimulus period. To investigate the amplitude of the N1, the data were rereferenced to Fz. First, the latencies of all laser-evoked responses were assessed for each participant using the average across all trials and conditions. We used a peak/trough detection procedure within the time windows 120 to 20, 180 to 30, and 250 to 500 ms (19) for the N1, N2, and P2, respectively. Second, to obtain the amplitudes of the average evoked responses, trials were averaged separately for each condition. Amplitudes of N1, N2, and P2 were assessed by averaging a 30-ms window centered at respective latencies determined in the previous step. Amplitudes of N1 and N2/P2 were extracted at channel C4 (79) and Cz, respectively. Finally, single-trial estimates of N1, N2, and P2 amplitudes were obtained according to averaging single-trial data across the same 30-ms windows centered at the latencies identified in step one. For the N1, three participants were excluded from statistical analyses due to a lack of a response in step one.

For the laser-evoked poststimulus responses, we were interested in prestimulus differences in brain activity induced by the expectation of high or low stimuli. Hence, we investigated the SPN by averaging the amplitude at Cz across the 500-ms interval directly preceding the laser stimulus (29). All HE and LE trials were averaged separately for each participant. A low-pass filter with a cutoff frequency of 30 Hz (fourth-order Butterworth) and a baseline correction using the time interval between ~3.3 and ~2.8 s were applied. No further high-pass filter was applied to avoid losing low-frequency information. As a consequence, five participants had to be excluded from this analysis due to sweating artifacts, which could be corrected by high-pass filtering when laser-evoked responses were analyzed.

Time-Frequency Analysis of EEG Data. To quantify the power of laser-induced evoked responses, data were transformed to the time–frequency domain. To this end, we applied a fourth-order Butterworth high-pass filter of 1 Hz and a band-stop filter of 49 to 51 Hz to dampen line noise. Subsequently, a fast Fourier transformation was applied to Hanning-tapered EEG data with a moving time window of 500-ms length for the frequencies from 1 to 30 Hz and a window of 250-ms length for the frequencies from 31 to 100 Hz. The step size was set to 20 ms. We chose a longer window for lower frequencies to retrieve more accurate power estimates, including at least four cycles for frequencies above 8 Hz. To obtain average responses at different frequency bands, time–frequency data were averaged across trials separately for each of the four conditions. Responses at alpha (8 to 12 Hz), beta (13 to 30 Hz (72)), and gamma (70 to 90 Hz (80)) frequency bands were quantified using the time windows 500 to 900, 300 to 600 (81, 82), and 150 to 350 ms (80), respectively. Alpha and beta power was estimated at sensors Cz, C2, C4, Cz, C2, and C4 covering the somatosensory cortex (19, 81, 82). Gamma power was obtained at sensor Cz. Sensors Cz, C2, C4, Cz, C2, and C4 were selected for response data. All power bands were calculated by estimating the mean power estimates across the selected frequencies, time windows, and channels (region of interest, ROI). Consequently, we obtained three power values for each condition (i.e., 12 power values for each participant). Single-trial responses of different frequency bands were quantified by averaging across the same time–frequency sensor selection as for the average responses for each trial. All power values were not baseline corrected (see SI Appendix, Table S1 for results with baseline correction using the interval ~750 to ~250 ms preceding the laser stimulus as baseline).

In addition to oscillatory poststimulus responses, we were interested in prestimulus differences in oscillatory brain activity induced by the expectation of hi or li stimuli. Prestimulus alpha (8 to 12 Hz) and beta (13 to 30 Hz) power were obtained using the mean power across the time windows ~2.5 to ~1.5 s as well as ~1.25 to ~0.25 s and the sensors Cz, C2, C4, Cz, C2, and C4. We chose these time windows to investigate power differences during cue presentation (~2.5 to ~1.5 s) and closely before laser stimulus onset (~1.25 to ~0.25 s). Data immediately preceding the laser stimulus were not analyzed to avoid confounding prestimulus power estimates with poststimulus activity due to the 500-ms sliding window.

Analysis of Skin Conductance Data. To quantify SCR, epochs of skin conductance data were averaged across trials for each condition and participant. Amplitudes were defined as peak amplitudes of the maximal peak within a time window from 1 to 7.8 s poststimulus following a peak detection
We used the R package BayesFactor [version 0.9.12 (86)] to compute BF$s for model comparisons. These BF$s quantify the evidence for one model over another model as a ratio of two likelihoods (i.e., the likelihood of the data given each model). Stimulus intensity was coded as 1 for hi stimuli and as 0 for li stimuli. Expectation was coded as the probability of a following hi stimulus [i.e., 0.75 for hi cue conditions (hiHE and liHE) and 0.25 for li cue conditions (hiLE and liLE)]. Finally, the PE was defined as aversive PE, meaning that a PE occurs only if the outcome (stimulus intensity) is more painful than expected. Specifically, the aversive PE was selected because a previous study by Geutert, Boll, Eippert, and Buchel (50) demonstrated that models incorporating the aversive PE explained brain responses to pain better than absolute and signed PEs. Hence, it was coded as difference between stimulus intensity and expectation [i.e., PE = 1 to 0.25 for hiLE, PE = 1 to 0.75 for hiHE, and PE = 0 for hiLE and liLE (50); see SI Appendix, Fig. S2 for Bayesian model comparisons using additional absolute and signed PE formulations].

To complement univariate analyses using single poststimulus responses as outcome variables and to investigate whether a combination of N1, N2, P2, alpha, beta, and gamma power can predict the expectation effect on pain ratings, we computed difference values of pain ratings, N1, N2, P2, alpha, beta, and gamma power by subtracting average values of the LE trials from HE trials for each participant. Subsequently, we tried to predict difference values of pain ratings (dependent variable) based on difference values of N1, N2, P2, alpha, beta, and gamma power using multiple regression. Prior to the analysis, all difference values were z-transformed across participants to adjust the data to the same scale.

Finally, we investigated whether cue-induced expectations affected brain activity preceding the laser stimulus. To this end, we performed Bayesian-dependent samples Student’s t tests comparing the average amplitude of the SPN between HE and LE trials. Similarly, we compared alpha and beta power during two prestimulus windows, one during cue presentation and one closely preceding the painful laser stimulus. Again, these tests were accompanied by Bayesian-dependent samples Student’s t tests to estimate the evidence for the null hypothesis. To test for additional effects outside the predefined ROIs, we performed cluster-based permutation tests across time, frequencies, and all channels (see SI Appendix for details).

Data Availability. All data in EEG-BIDS format (87) and code are available at the Open Science Framework (https://osf.io/jy8wv/).

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