

The Dynamics of Pain: Evidence for Simultaneous Site-Specific Habituation and Site-Nonspecific Sensitization in Thermal Pain

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Abstract: Repeated exposure to noxious stimuli changes their painfulness, due to multiple adaptive processes in the peripheral and central nervous systems. Somewhat paradoxically, repeated stimulation can produce an increase (sensitization) or a decrease (habituation) in pain. Adaptation processes may also be body-site-specific or operate across body sites, and considering this distinction may help explain the conditions under which habituation versus sensitization occurs. To dissociate the effects of site-specific and site-nonspecific adaptation processes, we examined reported pain in 100 participants during counterbalanced sequences of noxious thermal stimulation on multiple skin sites. Analysis of pain ratings revealed 2 opposing sequential effects: repeated stimulations of the same skin site produced temperature-dependent habituation, whereas repeated stimulations across different sites produced sensitization. Stimulation trials were separated by ~20 seconds, and sensitization was unrelated to the distance between successively stimulated sites, suggesting that neither temporal nor spatial summation occurred. To explain these effects, we propose a dynamic model with 2 adaptation processes, one site-specific and the other site-nonspecific. The model explains 93% of the variance in the group-mean pain ratings after controlling for current stimulation temperature, with its estimated parameters showing evidence for habituation for the site-specific process and sensitization for the site-nonspecific process. The 2 pain adaptation processes revealed in this study, and the ability to disentangle them, may hold keys to understanding multiple pain-regulatory mechanisms and their disturbance in chronic pain syndromes.

Perspective: This article presents novel evidence for simultaneous site-specific habituation and site-nonspecific sensitization in thermal pain, which can be disentangled (and the direction and strength of each process estimated) by a dynamic model. The dissociation of site-specific and site-nonspecific adaptation processes may hold keys to understanding multiple pain-regulatory mechanisms in both healthy and patient populations.

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Key words: Thermal pain, habituation, sensitization, dynamic model, somatotopic specificity.

Pain perception is strongly modulated by dynamic adaptive processes.^{6,25,41} Although the degree of pain is driven by the intensity of a noxious stimulus, there is also a substantial portion of variance arising from temporal adaptation processes that may or may not interact with stimulus intensity.^{21,23} Many chronic pain syndromes are characterized by disturbed

pain adaptation processes, such as a lack of habituation or abnormal sensitization,^{11,15,39,50,52,59} which may reflect an increased excitability of central⁶³ and/or peripheral¹⁶ nociceptive neurons. The temporal dynamics of pain, and the ability to estimate them accurately, may hold keys to understanding multiple mechanisms of pain regulation, as well as the development of chronic pain.^{3,9,15,50}

There are well-known dynamic effects in pain that occur during continuous or fast repetitive noxious stimulation, such as temporal summation^{13,17,24,29,34,41,42,54} and offset analgesia (the disproportionately large decrease in thermal pain following a slight decrease in stimulus temperature).^{19,64,65} Temporal pain adaptation also occurs during sequences of more widely spaced noxious stimuli (eg, separated by 10–80 seconds). Several studies have reported a rapid

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decrease in experienced pain over the course of such stimulus series,^{8,14,25,35} although increases in pain over time have also been reported.^{5,33} As is common in the pain literature, we will use the terms *habituation* and *sensitization* to refer to the general class of adaptive processes whereby current experienced pain is decreased or increased (respectively) by previous painful stimuli (note that some authors use habituation to refer only to nonsensorimotor mechanisms^{20,46,56}; we do not make that commitment here).

The variety of temporal pain adaptation effects implies the existence of multiple different pain adaptation processes. Because changes in pain ratings over the course of repeated noxious stimulation reflect the combined effects of these processes, dynamic effects can appear complex and their various components may be difficult to disentangle in standard statistical analyses. However, these effects may be well explained by dynamic models that capture the adaptation processes underlying these effects. For example, Cecchi et al⁶ recently developed a model of thermal-pain perception that can accurately predict the temporal evolution of continuous pain ratings during sustained heat stimuli, by modeling the various processes that underlie the transformation of thermal heat to pain perception. In the present study, we aimed to characterize the processes underlying sequential effects on pain ratings during series of repeated thermal stimuli.

One important factor that affects which pain adaptation processes predominate during repeated exposure to noxious stimuli may be whether these stimuli are applied to the same or to different body sites. It has been argued that site-specific and site-nonspecific effects reveal peripheral versus central adaptation processes, respectively¹⁸; however, this is not necessarily true: although pain adaptation effects that occur during successive stimulations of different body sites must indeed originate in the central nervous system, changes in pain produced by repeated stimulation of the same skin site can be either peripheral or central in origin. Nonetheless, different processes likely mediate changes in pain that occur during repeated stimulation of the same versus different body sites: a somatotopically specific adaptation process versus a more general adaptation process that operates across body sites. However, previous studies on the temporal dynamics of pain have largely neglected this distinction; hence, the respective directions (habituation or sensitization) of both types of adaptation effects remain to be explored. We dissociated site-specific and site-nonspecific pain adaptation effects by analyzing variations in reported pain during carefully counterbalanced sequences of repeated thermal stimuli on the same and different skin sites. We first examine the respective effects of site-specific and site-nonspecific repetition, and their interactions with stimulus intensity, using a standard regression analysis. We next propose a dynamic model to characterize the underlying processes of these effects.

Methods

Participants

One hundred healthy participants completed the experiment (mean age = 23.5, range = 18–52 years; 47 males, 38 females, 15 sex not reported; 84 right-handed, 4 left-handed, 2 ambidextrous, 10 hand dominance not reported). Participants reported no history of psychiatric, neurologic, or pain disorders, no current pain, and no intake of analgesics on the testing day. All participants gave informed consent and received \$12 per hour for their participation. The experiment was approved by the institutional review board of the University of Colorado, Boulder.

Procedure

Testing took place while the participant was sitting in a comfortable chair designed to reduce spontaneous movement. We applied a sequence of 24 thermal stimuli of 11 seconds each (peak temperature = 41–49°C; 1.75 seconds ramp up, 7.5 seconds at peak temperature, 1.75 seconds ramp down) to 8 sites on the volar surface of participants' left inner forearms, using a 16 × 16 mm Peltier thermode (Medoc Ltd, Ramat Yishai, Israel). The sites were organized in a 4 × 2 layout, as illustrated in Fig 1A, for 62 participants, and in an 8 × 1 layout (ie, 8 sites aligned in 1 line along the inner forearm) for 38 participants. Adjacent stimulation sites were separated by ~1 cm. The 24 stimuli were logically divided into 3 successive series of 8 stimuli. During each series, each of the 8 skin sites was stimulated once, in random order (Fig 1A).

Two seconds after each stimulus, participants used a computer mouse with their right hand to rate the overall amount of pain they experienced on that trial, on a 100-unit visual analog scale with anchors of *no pain* (0) and *worst-imaginable pain* (100).⁴³ Following the pain rating, the experimenter moved the thermode to another skin site, and then after a variable interval of 1 to 4 seconds the next thermal stimulus started. The interval between successive stimuli was approximately 20 seconds (including the time needed for the participant to make the overall-pain rating and for the experimenter to move the thermode to a new site). Thus, each skin site was stimulated 3 times, separated by 8 trials or ~4 minutes on average.

Each skin site received 1 low-temperature (41, 42, or 43°C), 1 medium-temperature (44, 45, or 46°C), and 1 high-temperature (47, 48, or 49°C) stimulus. In total, 1 low, 1 medium, and 1 high temperature were used twice and all other temperatures were used 3 times during the entire experiment. Between stimuli, the thermode maintained a baseline temperature of 32°C.

Regression Analysis

We conducted multilevel regression analyses on the pain ratings, using a customized version of Matlab's `glmfit` function (T.D.W.; `glmfit_multilevel`, which is part of the Multilevel Mediation Toolbox, available at <http://wagerlab.colorado.edu/tools>; see^{1,30,61} for

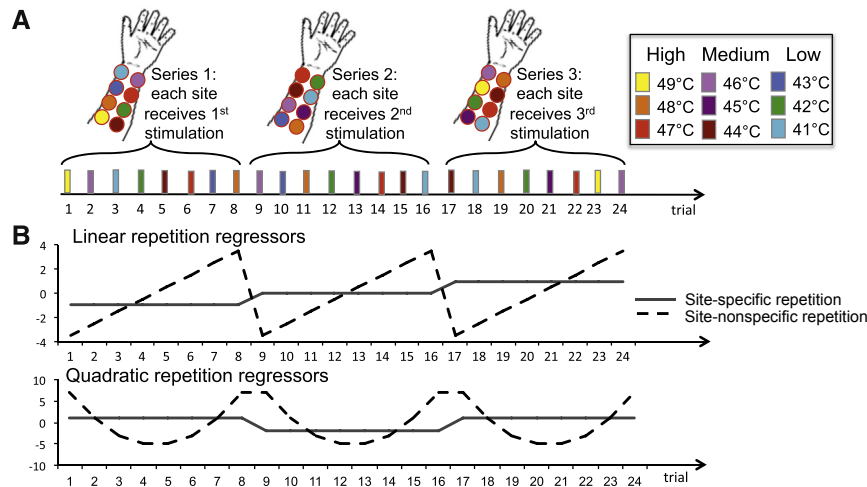


Figure 1. Repetition effects. **(A)** Design (stimulation sites not drawn to scale). The experiment consisted of 3 successive series of 8 trials. Within each series, we applied 8 successive thermal stimuli (11 seconds each, separated by ~20 seconds) to 8 different skin sites. Thus, in the first 8-trial series, each site is stimulated for the first time, whereas the second and third 8-trial series involve repeated stimulations of these same sites. **(B)** Repetition regressors. We modeled the linear and quadratic effects of site-specific repetition and site-nonspecific repetition (and their interactions, as well as the effects of temperature, and temperature by repetition interactions; not shown).

details on the implementation of our multilevel modeling procedures). We included regressors for the following effects of interest: temperature (9 levels), site-specific repetition (3 levels), and site-nonspecific repetition (8 levels). Fig 1B illustrates the repetition regressors. The site-specific repetition regressor indicated whether the currently stimulated skin site was stimulated for the first, second, or third time. We reset the site-nonspecific repetition regressor at the beginning of each 8-trial series in order to orthogonalize the regressors coding for site-specific and site-nonspecific repetition. We modeled these effects as continuous regressors, with linear and quadratic effects. To fully characterize the data, we also modeled the interactions between site-specific and site-nonspecific repetition. This resulted in a fully orthogonal set of regressors coding for site-specific repetition, site-nonspecific repetition, and their interactions. All regressors were centered, and all interaction regressors were calculated from centered variables.

To assess the dependence of temporal pain dynamics on the current stimulation temperature, we modeled the interactions between each repetition effect and current stimulation temperature. To assess the effects of the previous stimulation temperature, we conducted additional analyses that included a regressor coding for the temperature of either the immediately preceding stimulus or the most recent stimulus applied to the same site as the current stimulation.

After running the regression model including all above-mentioned regressors, we excluded the regressors that did not predict pain rating ($P_s > .1$) for our final regression model. We report the final model's results, which are very similar to those from the initial full model. We further examined the nature of the significant interaction effects using repeated-measures analyses of variance.

Dynamic Model

The above-described regression analyses test for the presence of site-specific and site-nonspecific repetition effects on pain ratings, but do not inform about the underlying processes that give rise to these effects. To address this issue, we developed a dynamic model that characterizes the effects of past thermal stimuli on reported pain (Fig 2). The model was implemented in Matlab (R2012a; Mathworks, Natick, MA). We will first

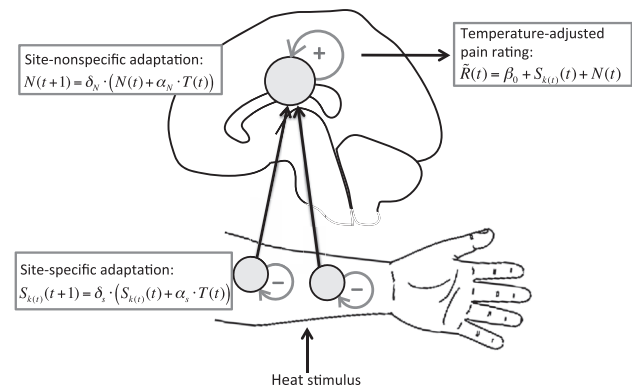


Figure 2. Illustration of the dynamic model. The model predicts trial-by-trial dynamics of temperature-adjusted pain rating $\hat{R}(t)$, that is, fluctuations in reported pain that are not due to variation in the current stimulus intensity. $\hat{R}(t)$ is modeled as a sum of site-nonspecific and site-specific adaptation processes, plus an intercept (β_0). To this end, the model assumes both a site-nonspecific state variable (N) and a site-specific state variable (S), which are both updated as a function of noxious input. Note that although we displayed site-specific adaptation at a peripheral level (on the stimulated skin sites), this is illustrative only; site-specific habituation may also have a central contribution. Similarly, although we display site-nonspecific adaptation in the cortex, we do not know where in the central nervous system this effect arises (this could be in the spinal cord, brainstem or cortex).

provide a qualitative description of the model, followed by its algorithmic details.

Qualitative Description of the Model

Our model assumes that each time someone receives a thermal stimulus, that person's pain sensitivity, and therefore the degree of pain she or he perceives in response to subsequent stimuli, is dynamically updated. Thus, the perceived pain induced by a thermal stimulus depends on the number and intensity of previous stimuli. To allow different temporal dynamics for site-specific and site-nonspecific repetition, each thermal stimulus updates both the sensitivity level of the specific skin site it is applied to and a general site-nonspecific sensitivity level. Both updating processes can cause either habituation (decreased sensitivity) or sensitization (increased sensitivity), depending on the direction of the updating process, and the overall effect of past stimuli on perceived pain is defined as the sum of both effects. Thus, the site-specific and site-nonspecific adaptation processes can (partially) cancel each other out if they are in opposite directions and are additive if they are in the same direction.

The direction and strength of each updating process are determined by the model parameter α (α_S for the site-specific adaptation, and α_N for the site-nonspecific adaptation): negative values of α result in habituation and positive values of α result in sensitization, and both effects are stronger for larger absolute values of α . Because it has been reported that high-intensity heat stimuli produce stronger subsequent pain adaptation than low-intensity stimuli,²⁸ our model assumes that the degree of sensitivity updating following a thermal stimulus also depends on the intensity of that stimulus. To this end, the change in sensitivity following a heat stimulus is scaled by the intensity of that stimulus.

Because pain habituation and sensitization are nonlinear processes, which have been shown to asymptote after a certain number of stimuli,^{25,32} our model allows both updating processes to asymptote after a certain number of stimulus repetitions. This is implemented in the model through an exponential decay process, which rate is controlled by model parameter δ (δ_S for the site-specific process and δ_N for the site-nonspecific process, allowing different decay rates for the 2 updating processes).

To summarize, our model assumes that past thermal stimuli affect stimulus-evoked pain through 2 dynamic processes: 1) a sensitivity-updating process, which causes someone's sensitivity to thermal stimuli to increase or decrease with repeated stimulation (controlled by model parameter α), and 2) a decay process, which allows this updating process to asymptote after a sufficient number of stimuli (controlled by model parameter δ). Two copies of these processes operate in parallel, on the sensitivity level of the currently stimulated skin site and on a general, site-nonspecific sensitivity level.

Finally, we would like to note the similarity and differences between our model and a recently proposed model of pain dynamics during individual periods of continuous thermal stimulation.⁶ Cecchi et al⁶ developed a dynamic model that can explain a variety of temporal effects on continuous pain ratings during sustained thermal stimuli, including offset analgesia. Their model includes a temperature-dependent "force" and a decay term, which are functionally similar to the α and δ parameters of our model, respectively. In addition, the Cecchi et al model contains a "dynamic-restoring force" that captures the effects of fast changes in stimulus intensity; because we did not model moment-by-moment pain dynamics during individual stimuli, our model did not include this component. An important novel feature of our model is that it assumes that the same qualitative dynamics work in parallel on site-specific and site-nonspecific adaptation processes.

Quantitative Description of the Model

In our model, each skin site, k , is associated with a state variable, S_k , which characterizes that site's level of sensitization or habituation at any given time and is dynamically updated as a function of noxious input. If $S_k > 0$, then stimuli at site k will be perceived as more intense than normal (somatotopic sensitization), and if $S_k < 0$, then stimuli will be perceived as less intense than normal (somatotopic habituation). The model also assumes a site-nonspecific state variable, N , which represents general habituation ($N < 0$) or sensitization ($N > 0$) across all sites. N is also dynamically updated as a function of noxious input. Thus, the S_k and N state variables can separately capture site-specific and site-nonspecific pain dynamics.

The purpose of the model is to predict the trial-to-trial dynamics of pain as a function of a sequence of noxious stimuli, above and beyond effects of the stimulus intensity itself. Thus, we define the *temperature-adjusted pain rating*, $\tilde{R}(t)$, as the residual on trial t obtained by regressing each participant's pain ratings on the linear and quadratic Temperature predictors. This adjusted pain rating is then modeled as a sum of site-specific and site-nonspecific sequence effects, plus an intercept (β_0):

$$\tilde{R}(t) = \beta_0 + S_{k(t)}(t) + N(t) \quad (1)$$

Here, $k(t)$ is the site stimulated on trial t , and $S_{k(t)}(t)$ and $N(t)$ are the current levels of site-specific and site-nonspecific sensitization (if positive) or habituation (if negative).

The remainder of the model concerns the dynamics of S and N . The value of each of these variables reflects effects of past stimuli—stimuli applied to each separate site in the case of S and all stimuli in the case of N —that are assumed to decay exponentially across time. S and N are each governed by 2 free parameters, α_S and δ_S , and α_N and δ_N , respectively. Following each trial t , the state of adaptation at the stimulated site, $S_{k(t)}$, is incremented in proportion to the current temperature, with a constant of proportionality determined by α_S .

We defined current temperature as the difference between the stimulus temperature and the baseline temperature (ie, T = stimulus temperature minus 32°C), so that the baseline temperature produces no adaptation. In the interval between trials t and $t + 1$, S_k is assumed to decay toward zero at a rate determined by δ_S , which is constrained to lie between 0 and 1 (a smaller value of δ_S indicates a faster decay rate). These assumptions lead to the following dynamics for S :

$$S_k(t+1) = \begin{cases} \delta_S \cdot (S_k(t) + \alpha_S T(t)) & k = k(t) \\ S_k(t) & k \neq k(t) \end{cases} \quad (2)$$

Thus, α_S determines the direction and magnitude of the sensitization/habituation effect. If $\alpha_S > 0$, then stimulation of a skin site results in sensitization, whereas if $\alpha_S < 0$, then stimulation results in habituation. δ_S determines the rate of decay, or the effective timescale of site-specific sensitization/habituation.

The site-nonspecific adaptation state, N , follows the same dynamic principles. Because N is affected by stimulation at all skin sites, it is incremented by the stimulus on every trial, by an amount proportional to the current temperature and a magnitude parameter α_N . Then it decays between trials with rate δ_N (constrained to lie between 0 and 1). Therefore, the dynamics for N are described by

$$N(t+1) = \delta_N \cdot (N(t) + \alpha_N \cdot T(t)) \quad (3)$$

As with site-specific adaptation, δ_N determines the decay rate or effective timescale of site-nonspecific sensitization/habituation (a smaller value of δ_N indicates a faster decay rate), and α_N determines its direction and magnitude, with $\alpha_N > 0$ producing site-nonspecific sensitization and $\alpha_N < 0$ producing site-nonspecific habituation.

Model Estimation

We estimated the 4 parameters of the dynamic model by minimizing the sum of the squared error between the observed trial-by-trial temperature-adjusted pain ratings and those predicted by the model. To optimize the parameter fits, we used Matlab's `fmincon` function,⁷ a constrained nonlinear optimization algorithm, with 30 randomized starting parameter estimates. We fitted the model separately to each participant's data, to obtain estimates of each parameter per participant ($\hat{\alpha}_N$, $\hat{\alpha}_S$, $\hat{\delta}_N$, and $\hat{\delta}_S$). We tested whether $\hat{\alpha}_N$ and $\hat{\alpha}_S$ (the signed magnitude parameters of the site-nonspecific and site-specific temporal adaptation, respectively) significantly differ from 0 by means of 1-sample t-tests.

After fitting the model to each participant's individual data, we computed the *group-mean* observed and model-predicted temperature-adjusted pain ratings on each of the 24 trials. The group-averaged trial-by-trial data contain much less noise than the single-trial data in individual participants, especially given our large number of participants ($N = 100$). Therefore, a comparison of the observed and model-predicted group-mean data indicates how well the model explains the *systematic* pattern of trial-by-trial dynamics in pain ratings.

Model Comparison

We tested the advantage of our model over simpler models that assume only site-specific ("site-specific-only model") or only site-nonspecific ("site-nonspecific-only model") dynamics. We created these simpler models by removing either the $N(t)$ or the $S_{k(t)}(t)$ term from the full model (Equation 1), that is, by setting $N(t) = 0$ in the site-specific-only model or $S_{k(t)}(t) = 0$ in the site-nonspecific-only model. We then compared the proportion of variance explained by the full model with those explained by each of the 2 simpler models.

Results

Fig 3A shows 5 randomly selected participants' pain ratings on every trial of the experiment. Note that each of 8 skin sites received its first stimulation during trials 1 to 8, and its second and third stimulations during trials 9 to 16 and 17 to 24, respectively. Whereas the effects of stimulus temperature are easily noticeable in these plots, the effects of temporal adaptation are more difficult to detect because of the trial-by-trial variation in stimulus temperature and the noise inherent in single-trial/single-participant data. To examine the systematic changes in pain ratings over the course of the 24 stimulation trials, above and beyond effects of stimulus intensity, we regressed out the effects of temperature (ie, we removed the variance in pain ratings that was accounted for by the linear and quadratic effects of temperature) and plotted the group-mean temperature-adjusted pain ratings on each trial of the experiment (Fig 3B). Fig 3B indicates that 1) there was an overall decrease in pain ratings across the 3 successive 8-trial series (site-specific habituation), and 2) pain ratings gradually increased (site-nonspecific sensitization) during the first, but not during the second and third, stimulation series. We will formally test these observations in the next 2 subsections, using a multilevel regression analysis and our dynamic model, respectively.

Regression Results

Table 1 summarizes the effects of all significant predictors of pain ratings from the regression analysis.

Effects of Current Stimulus Intensity

As expected, pain ratings increased with increasing temperature, as reflected by the positive effects of temperature (Table 1; Fig 4). There were both linear and quadratic effects of temperature, suggesting a nonlinear relationship between pain rating and temperature that is consistent with previous studies.^{27,57}

Site-Specific Adaptation Effects

Fig 4 shows the group-mean pain ratings for the first, second, and third site-specific stimulation (ie, the grand-average pain ratings for trials 1–8, 9–16, and

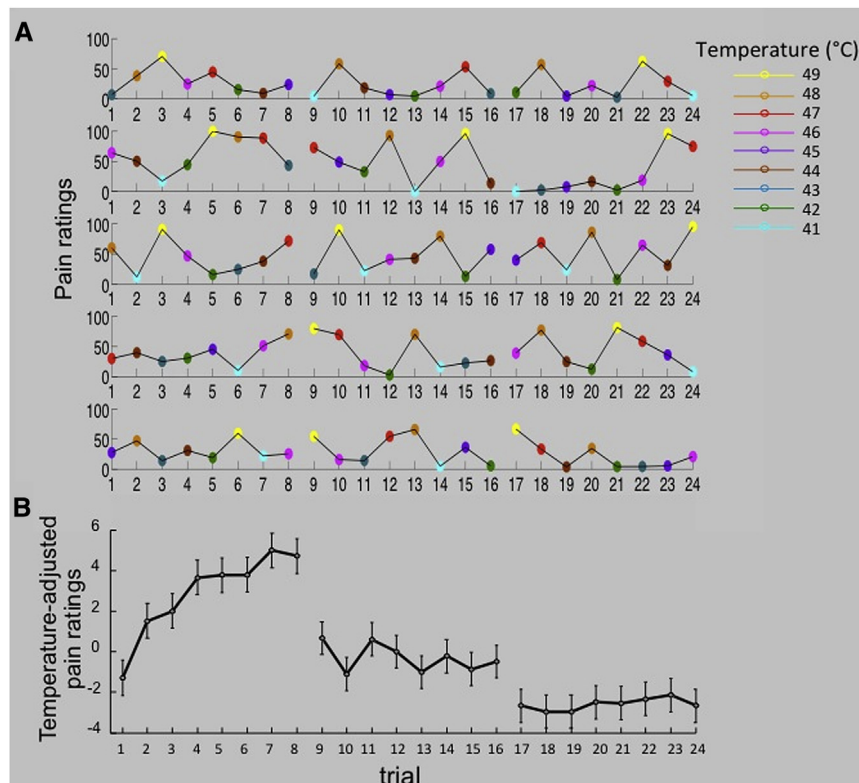


Figure 3. (A) Pain ratings on each trial of the experiment, color-coded for stimulus temperature, for 5 randomly selected participants. Note that in the first 8-trial series each of 8 skin sites are stimulated for the first time, whereas the second and third 8-trial series involve repeated stimulations of these same sites. (B) The group-mean temperature-adjusted pain rating on each trial of the experiment. We obtained temperature-adjusted pain ratings by taking the residuals from a regression of pain rating on the linear and quadratic effects of temperature. Error bars are within-subject standard errors of the means.³¹

17–24, respectively), as a function of current stimulus temperature. The regression analysis revealed a negative linear effect of site-specific repetition

Table 1. Predictors of Pain Rating

	COEFFICIENT	SEM	COHEN'S			P
			D	T		
Intercept	25.12 (13)	1.29	1.9	19.4	< .001	
Temperature effects						
Temperature L	5.99 (2.6)	.25	2.3	23.57	< .001	
Temperature Q	.68 (.46)	.04	1.5	15.59	< .001	
Repetition effects						
Site-specific L	−2.56 (3.9)	.38	.65	−6.81	< .001	
Site-nonspecific L	.24 (.97)	.09	.25	2.59	.01	
Specific L × nonspecific L	−.24 (1.2)	.11	.21	−2.17	.03	
Specific Q × nonspecific L	.21 (.77)	.07	.27	3	.004	
Specific L × nonspecific Q	.11 (.48)	.05	.20	2.27	.03	
Current temperature × repetition interactions						
Temperature L × specific L	.58 (1.1)	.11	.53	5.38	< .001	
Temperature L × specific Q	−.13 (.48)	.05	.24	−2.82	.006	
Temperature Q × specific L	.31 (.43)	.04	.75	7.63	< .001	

Abbreviations: SEM, standard error of the mean; L, linear effect; Q, quadratic effect.

NOTE. Standard deviations are in parentheses.

(Table 1), reflecting the decrease in pain ratings across the three 8-trial series for most stimulus intensities. Because the site-specific repetition regressor was correlated with overall trial number, this effect could in principle be due to either site-specific habituation or a persistent site-nonspecific trial-by-trial habituation. However, the absence of evidence for a site-nonspecific habituation effect (but instead an increase in pain ratings during the first series; see next section) suggests that this effect was due to site-specific habituation.

There were also significant site-specific repetition × current temperature interactions (Table 1), reflecting that the site-specific habituation effect was strongest for low temperatures, and reversed for high temperatures (Fig 4). To further examine these interactions, we tested the site-specific repetition effect separately for each level of current stimulation temperature, using repeated-measures analyses of variance. These analyses revealed that repeated stimulation of the same skin site resulted in a significant decrease in pain rating for 41 to 47°C stimuli ($F[2, 140] = 20.8$, $F[2, 142] = 16.7$, $F[2, 112] = 34.8$, $F[2, 128] = 30.5$, $F[2, 120] = 17.9$, $F[2, 146] = 14.4$, $F[2, 134] = 10.5$, respectively, all P s < .001), no significant effect for 48°C stimuli ($P = .43$), and a significant increase in pain rating for 49°C stimuli ($F[2, 129] = 9.6$, $P < .001$).

Finally, we examined the interactions of site-specific repetition with previous stimulus temperature. To this end, we extended the regression model with a regressor

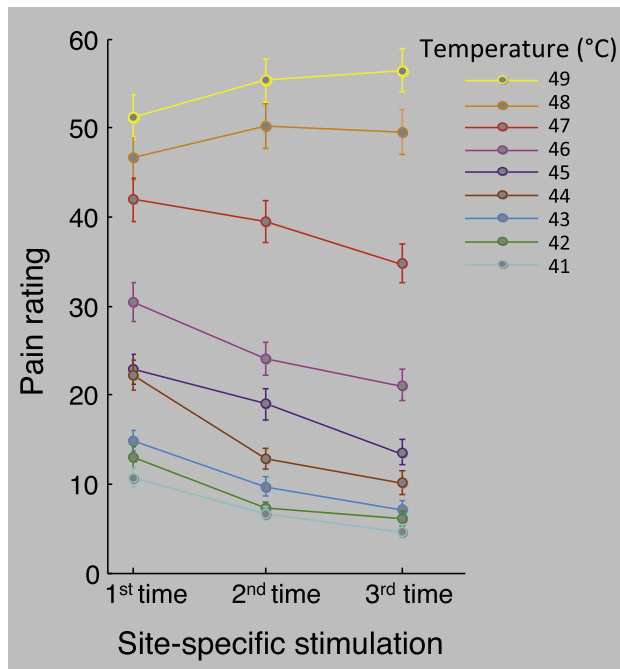


Figure 4. Group-mean pain ratings as a function of current stimulus temperature and site-specific repetition. The first, second, and third site-specific stimulation correspond to stimulation trials 1–8, 9–16, and 17–24, respectively. The average number of participants that contributed to each data point was 89 (range = 81–95, because for each participant 3 of the temperatures were used twice and all other temperatures were used 3 times; see Methods section). Error bars are between-subjects standard errors of the means.

coding for the temperature of the most recent stimulus applied to the same site (on average, 8 trials ago). In this model, we excluded trials 1 to 8, for which there were no previous stimulations on the same site. This analysis revealed that higher-intensity stimuli produced greater subsequent site-specific habituation when the same site was stimulated again ($\beta = -.51$, $t = -4.14$, $P < .001$). The effect of previous stimulus temperature did not interact with current stimulus temperature ($\beta = -.09$, $t = -1.55$, $P = .12$).

Site-Nonspecific Adaptation Effects

In contrast to the (temperature-dependent) site-specific habituation, the regression analysis revealed a significant linear *increase* in pain rating during successive stimuli applied across different skin sites (site-nonspecific sensitization; Table 1). Site-nonspecific repetition did not interact with current stimulus temperature ($ps > .1$).

There were also several site-nonspecific repetition \times site-specific repetition interactions (Table 1), reflecting that the site-nonspecific sensitization was restricted to the first 7 to 8 trials of the experiment (Fig 3B). We conducted follow-up repeated measures analyses of variance on temperature-adjusted pain ratings to examine the site-nonspecific repetition effect separately for each of the 3 levels of site-specific repetition (ie, separately for trials 1–8, 9–16, and 17–24). These analyses revealed a highly significant increase in pain during the first 8-trial series ($F[7, 693] = 5.76$, $P < .001$), but no sequential effects during

the second and third 8-trial series ($Ps > .6$). Thus, successive stimuli applied to different skin sites only produced sensitization when the sites were stimulated for the first time. There are at least 2 possible explanations for this restriction of site-nonspecific sensitization to the first 8 stimulation trials: 1) repeated stimulation on a site may have abolished this effect, and 2) site-nonspecific sensitization may have reached asymptote after ~ 8 of the stimuli used in our experiment.

We also tested whether site-nonspecific sensitization depended on the intensity of the preceding stimulus. To this end, we extended the regression model with a regressor coding for the temperature of the immediately preceding stimulus, which was nearly always on a different skin site. In this model we excluded the first trial. This analysis revealed that higher-intensity stimuli produced greater sensitization on the following stimulation trial ($\beta = .26$, $t = 2.9$, $P = .005$). Thus, whereas higher-intensity stimuli produce greater site-specific habituation (see previous section), they also produced greater site-nonspecific sensitization.

The site-nonspecific sensitization during the first series of stimuli might be explained by peripheral sensitization of the skin adjacent to the previously stimulated site. If so, we would expect to observe greater sensitization when the current and previous stimulation sites are closer together, and when the preceding stimulus is more intense. We tested these predictions on the pain-rating data from the first 8 stimulation trials, using a multilevel regression model with regressors coding for the distance between the current and previous stimulation site, current stimulus temperature, previous stimulus temperature, and the distance \times previous temperature interaction. Neither distance, nor the distance \times previous temperature interaction, significantly predicted pain rating ($Ps > .6$), suggesting that the site-nonspecific sensitization could not be explained by a peripheral sensitization process. That the distance between successive stimulation sites did not affect pain ratings also suggests that the successive stimuli in our experiment did not result in a spatial-summation-like effect (ie, higher perceived pain for larger areas of noxious stimulation,⁴⁴ which has been shown to be restricted to simultaneous inputs to nearby skin sites¹²).

Sex Effects

Previous studies have shown stronger habituation effects in women than in men.^{12,22} To examine whether any of the revealed effects were driven by either the male or the female participants, we included sex as a between-subjects factor in the regression analysis (excluding the 15 participants whose sex was unknown). Controlling for sex did not change the significance of any of the predictors of pain rating reported in Table 1. However, this analysis did reveal a sex \times site-specific repetition interaction, reflecting that the female participants showed stronger site-specific habituation ($\beta = .9$, $t = 2.37$, $P = .02$), in line with previous findings.^{12,22} This analysis also revealed a main effect of

sex, reflecting higher pain ratings in the female participants ($\beta = -3.3$, $t = 2.38$, $P = .02$), and a marginally significant sex \times linear-temperature interaction, reflecting that the female participants' pain ratings tended to be more strongly affected by stimulus temperature ($\hat{\beta} = -.52$, $t = 1.84$, $P = .069$). None of the other regressors interacted with sex. We next conducted separate regression analyses for the male and female participants to test the presence of site-specific habituation in both groups. These analyses revealed highly significant effects of site-specific repetition in both groups ($\beta = -1.63$, $t = 3.87$, $P < .001$, and $\beta = -3.5$, $t = 5.31$, $P < .001$, for the male and female participants, respectively). Thus, although site-specific habituation was stronger in the female participants, it was clearly present in the male participants as well.

Dynamic-Model Results

The linear and quadratic effects of stimulus temperature explained on average 79% of each individual participant's trial-by-trial pain ratings. We examined how much of the residual variance (21%) could be accounted for by the temporal dynamics captured by our dynamic model. To this end, we fitted the model to the temperature-adjusted pain ratings of each individual participant. Fig 5 (upper panel) shows the group-mean temperature-adjusted pain ratings on every trial of the experiment, as well as those predicted by the dynamic model. The model explained 93% of the variance in group-mean temperature-adjusted pain ratings across trials, suggesting that it accurately captured the pattern of systematic dynamic effects across trials, including the

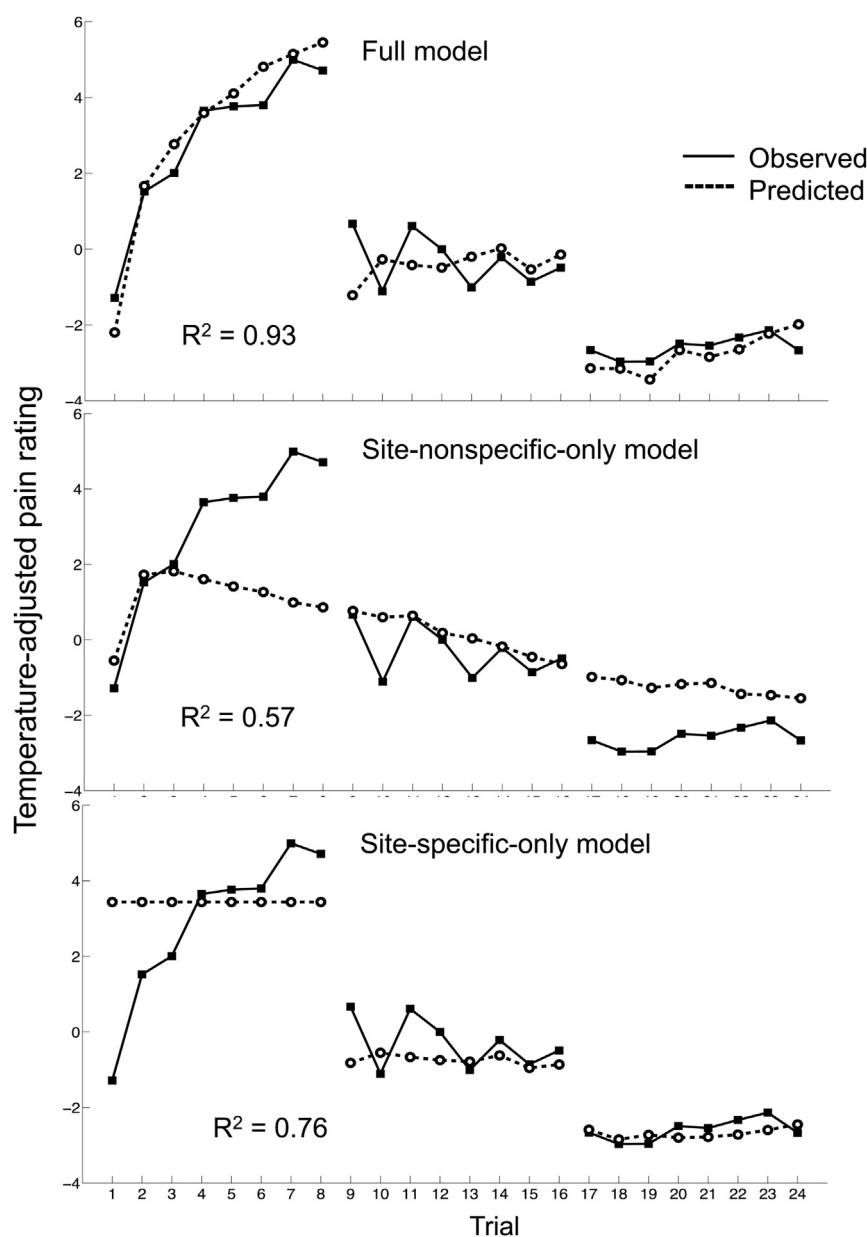


Figure 5. The group-mean temperature-adjusted pain ratings on each trial (straight lines), and those predicted by the full dynamic model and 2 simpler models that capture only site-nonspecific or only site-specific dynamics (dotted lines).

nonlinear, temperature-dependent effects captured in the standard regression analyses. The single-trial data from individual participants were, naturally, considerably noisier than the group-mean data; hence, fitting the model to individual participants' data resulted in less accurate predictions. The model still performed reasonably well, however, explaining on average 34% of the variance in individual, temperature-adjusted per-trial pain ratings (the remainder of the variance is presumably nonsystematic noise in single-trial ratings or reflects other processes not captured by the model). Fig 6 shows the per-trial temperature-adjusted pain ratings in 4 individual participants. It can be seen that through different values of the estimated model parameters, the model is able to capture a variety of different adaptation effects.

Table 2 shows the mean parameter estimates for fits of the model to each participant's data. $\hat{\alpha}_N$ was positive for 74 of the 100 participants, and mean $\hat{\alpha}_N$ was significantly greater than 0, $t(99) = 2.2$, $P = .027$, indicating site-nonspecific sensitization. By contrast, $\hat{\alpha}_S$ was negative for 86 of the 100 participants, and mean $\hat{\alpha}_S$ was significantly less than 0, $t(99) = -3.6$, $P < .001$, indicating site-specific habituation. The decay rates $\hat{\delta}_N$ and $\hat{\delta}_S$ were not significantly different from each other, $t(99) = 1.3$, $P = .21$.

Finally, we compared the fit of our model with those of 2 simpler control models that capture only site-nonspecific or only site-specific dynamics (Fig 5; Table 2). Whereas the full model predicted 93% of the variance of the group-mean data, the site-nonspecific-only and site-specific-only models predicted 57% and 76%, respectively. At the level of individual participants, the full, site-nonspecific-only, and site-specific-only models predicted on average 34%, 18%, and 19% of the variance, respectively. Thus, a combination of site-specific and site-nonspecific dynamics explains the data considerably better than either one of these alone.

Discussion

Much of the variation in pain report is driven by variation in noxious stimulus intensity, but substantial adaptation effects—sequential effects of the stimulation history—can also strongly modulate pain. Adaptation effects include both habituation and sensitization across time and may vary in their direction and magnitude across individuals. Predicting and explaining these dynamic effects may be clinically useful and may also help prevent confounds between experimental manipulations and dynamic adaptation processes in research studies.

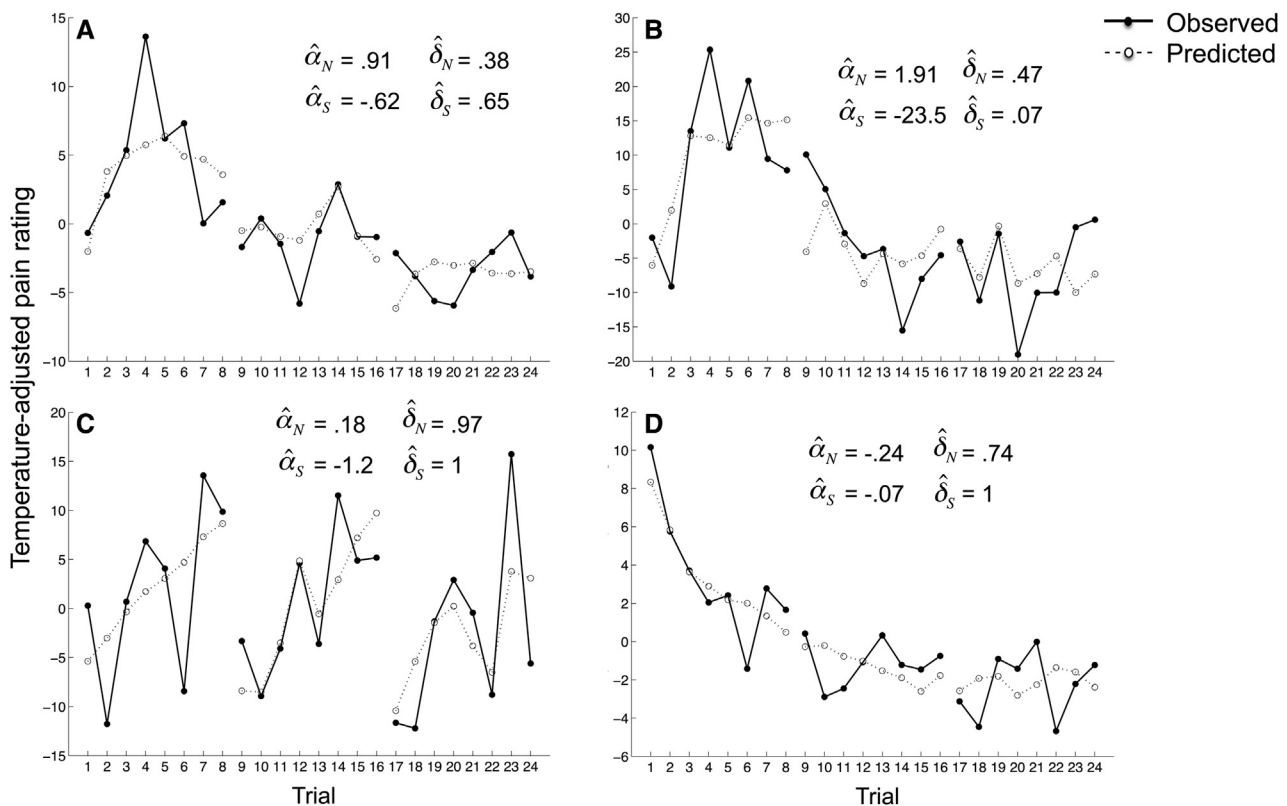


Figure 6. Per-trial temperature-adjusted pain ratings of 4 individual participants. The estimated parameters from fits of our dynamic model to each participant's data, and the pain ratings predicted by the dynamic model (dotted lines) are shown as well. Participants A and B are representative of the group-mean data: they show site-specific habituation, that is, pain ratings decrease across the three 8-trial series when stimuli return to the same skin sites, and site-nonspecific sensitization during the first ~4 stimuli. Participant C also demonstrates site-specific habituation and site-nonspecific sensitization but shows almost no decay of these processes, reflected in δ values of (almost) 1. This produces almost identical site-nonspecific sensitization effects during each 8-trial series, and a similar drop in pain ratings at the beginning of the second and third 8-trial series (when stimuli return to the same skin sites for the first and second times). Unlike most participants, participant D shows both site-specific and site-nonspecific habituation, reflected in a negative α_S and α_N , which produces a decrease in pain ratings both within and across the three 8-trial series.

Table 2. Mean Parameter Estimates for the Fit of the Full Dynamic Model and the 2 Simpler Control Models to Each Participant's Data, and the Proportion of Variance Explained by Each Model (R^2)

PARAMETER	FULL MODEL	SITE-NONSPECIFIC-ONLY MODEL	SITE-SPECIFIC-ONLY MODEL
α_N	8.74 (1.0 to 16.5)	5.87 (−4.8 to 16.6)	
α_S	−18.0 (−28.0 to −8.0)		−14.6 (−26.3 to −3.0)
δ_N	.55 (.48 to .63)	.47 (.39 to .55)	
δ_S	.49 (.40 to .57)		.48 (.39 to .56)
R^2 group-mean	.93	.57	.76
R^2 individual participants	.34	.18	.19

NOTE. Values are mean (95% confidence interval).

By dissociating site-specific and site-nonspecific adaptation processes, we found novel evidence for 2 opposing types of temporal dynamics in thermal pain. Repeated thermal stimulation on the same skin site produced habituation for all but the highest stimulation temperatures. In contrast, repeated stimulation across different skin sites produced sensitization. To parsimoniously explain these effects, we constructed a dynamic model that captures both types of adaptation processes. The model explained nearly all of the systematic trial-by-trial variance in pain ratings that remained after controlling for stimulus intensity. Because the model parameters were designed to reflect the underlying processes that give rise to temporal dynamics, they have a straightforward interpretation. In particular, α_S and α_N reflect the signed magnitudes of site-specific and site-nonspecific adaptation, respectively. These processes may manifest in multiple effects in standard statistical tests, which model the form of the data rather than its underlying processes. For example, the site-nonspecific sensitization effect that is only apparent in the first series of stimuli (the first 8 trials) produced complex site-specific \times site-nonspecific interactions in our regression analysis, but can be explained relatively parsimoniously by the decay parameter of the model's site-nonspecific adaptation process. That is, the model predicts that habituation/sensitization processes eventually saturate, which is why site-nonspecific sensitization was only observed during the first third of the stimulation trials. Thus, the model parameters complement standard statistical tests and provide additional insight into the temporal dynamics of thermal pain.

Site-specific habituation in this study depended on stimulus intensity in 2 ways: More-intense stimuli produced stronger habituation for *subsequent* stimulations on the same skin site, but more-intense (48–49°C) stimuli also reversed the habituation effect on the *current* trial, resulting in sensitization for the highest-intensity stimuli (more current pain for stimulations on previously stimulated sites). By suppressing mild repeated pain, while still allowing more biologically salient stimuli—which may, for example, signal tissue damage—to get through, habituation for low- and sensitization for high-intensity current stimuli may serve an important adaptive role in optimizing survival behavior. This contrastive behavior is characteristic of systems under a balance of excitatory and inhibitory control, such as

thalamic circuits that allow salient or attended visual percepts to get through while reducing background noise.^{48,49}

If reported pain indeed reflects a mix of site-specific habituation and site-nonspecific sensitization processes, as our data suggest, this has important implications for experimental pain protocols. These opposing repetition effects may cancel each other out in some paradigms but not in others, depending on the timing, stimulus intensity, and number of times the same versus new skin sites are stimulated. When habituation and sensitization processes are equally strong, 2 opposing effects may produce an apparent lack of temporal pain modulation. When one of the effects predominates, temporal dynamics may confound experimental pain modulation effects, especially those that develop over time (eg, expectancy, learning and placebo effects) and those that systematically covary with presentation order or stimulus intensity. Such temporal confounds can be minimized by carefully matching the use of new and previously stimulated sites across experimental conditions.

Disturbed pain adaptation processes play a key role in the pathophysiology of chronic pain. Patients with several chronic pain conditions (eg, fibromyalgia, migraine, and chronic back pain) show reduced habituation, or abnormal sensitization instead of habituation, to repeated noxious stimuli, which is reflected in both their subjective pain and pain-related brain activation.^{11,15,39,50,52,59} Whether deficient pain habituation is a *pre-dispositional factor* that contributes to the development and/or persistence of chronic pain or the *result* of an altered cortical state caused by the chronic pain is a matter of debate.^{10,51} Different studies have attributed habituation deficits in chronic pain patients to either cortical hyperexcitability or a reduced baseline level of cortical activity leading to heightened stimulus-evoked responses.⁹ In addition to abnormal central adaptation, peripheral input to the central nervous system (eg, nociceptor sensitization¹⁶) also appears to play a crucial role in the initiation and maintenance of chronic pain.^{40,45,55,60} Our dynamic model may be helpful in disentangling the underlying processes that give rise to pathologic pain.

Although most of our participants showed site-specific habituation and site-nonspecific sensitization, this was not the case for everyone (see Fig 6). Thus, even within the healthy population, there is considerable interindividual variability in the temporal dynamics of pain. These

individual differences may reflect interindividual variability in the sensitivities and/or decay rates of the site-specific and site-nonspecific adaptation processes. A recent study examining the effects of repeated noxious thermal stimulation over the course of several days also found remarkable individual differences in pain adaptation: Half of the participants showed habituation and the other half showed sensitization of their pain ratings.⁵³ Furthermore, those who sensitized, but not those who habituated, showed a reduction in gray matter density in several pain-processing brain regions on the last compared to the first stimulation day. Interestingly, similar reductions in gray matter density have been reported in chronic pain patients,³² suggesting that pain sensitization (in this case across several days of noxious stimulation) may indicate an increased risk for chronic pain development. Indeed, initially acute pain following an injury can transform into chronic pain when nociceptor sensitization persists after resolution of the injury or when this triggers a prolonged increase in the excitability and synaptic efficacy of central nociceptive neurons (central sensitization).^{62,63} As our dynamic model parameters reflect individuals' tendency to habituate/sensitize, another potential application of the dynamic model is the prediction of individuals' risk for chronic pain development. Although the present study was not designed to explain individual differences, the dynamic model we developed can capture pain adaptation effects at the group-mean level and provide estimates at the level of individual participants, thereby providing a foundation for assessment of individual differences. Future studies may measure person-level variables (eg, pain history, psychopathology) that could serve as predictors of individual differences in pain adaptation and relate these to individual participants' estimated pain adaptation rates.

Although our results provide strong evidence for the existence of 2 distinct and opposing pain adaptation processes, the biological basis of these processes remains to be explored in future studies. The site-nonspecific sensitization effect most likely reflected central mechanisms, especially given its independence on the distance between successive stimulation sites. The site-specific habituation effect, on the other hand, could reflect peripheral and/or central processes. It is interesting to note that the characteristics of our observed site-specific habituation effect show a striking resemblance to the response dynamics of monkeys' nociceptive afferent fibers during repeated heat stimulation.^{28,38,41,58} The heat-evoked response of these nociceptive fibers rapidly decreases during the first ~5 stimuli, with the strongest decrease from the first to the second stimulus. This suppressive effect of previous stimuli on nociceptive fibers' responsivity increases with the intensity of the preceding heat stimulus and takes more than 4 minutes to recover.²⁸ These similarities between activity of peripheral nociceptive fibers and our site-specific habituation effect support the idea that site-specific habituation is, at least partly, peripheral in origin. However, our data do not provide conclusive evidence about this matter, and site-specific adaptation effects may also arise in the central nervous

system. Site-specific habituation could, for example, originate from the suppression of pain-related activity in somatotopically organized spinal or cortical areas of the ascending pain pathway. Alternatively, if information about the stimulation sites is represented in the brain, site-specific habituation may be mediated by a descending pain-modulatory system that is somatotopically directed, perhaps similar to that underlying local placebo analgesia.^{4,37}

Neuroimaging studies could shine more light on the brain mechanisms underlying pain habituation and sensitization. A few studies have investigated the brain activation associated with pain adaptation during repeated stimulation,^{2,5,14,36} as well as the role of the opioid system,^{14,26,47} but these studies did not dissociate site-specific and site-nonspecific effects. Pain adaptation processes that are mediated at a peripheral level are expected to nonspecifically affect activation within all regions of the pain-processing network (similar to stimulus-intensity effects), whereas centrally mediated effects are likely associated with more specific activation, either within or outside the pain-processing network.

It remains to be explored whether the distinct effects of site-specific and site-nonspecific repetition generalize to other types of pain—for example, mechanical and electrical—and to other repetition rates. One caveat to the present experiment is that site-specific stimulations were separated by longer intervals than site-nonspecific stimulations, which may have influenced the results. However, we have preliminary data suggesting that site-specific habituation and site-nonspecific sensitization also occur during a stimulation protocol in which the same site is stimulated several times in a row before moving to the next site, which implies that our results were not due to the specific timings used in this experiment. Finally, we examined pain modulation effects during a relatively limited number of trials; hence, we did not address adaptation effects that may occur during longer sequences of repeated stimulation. A recent study showed that experienced pain during longer series of repeated heat stimuli applied to the same skin site follows a biphasic time course, with initial habituation followed by sensitization.²⁵ Whether or not these 2 effects arise from the same underlying processes, and whether they can be predicted by our dynamic model, are interesting questions for future research.

To conclude, our results reveal complex, but systematic, temporal dynamics of pain, which can be well explained by a relatively simple dynamic model. The ability to disentangle site-specific and site-nonspecific dynamic effects may serve to uncover the mechanisms underlying both normal and pathologic pain and could eventually contribute to the diagnosis and treatment of pain disorders.

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