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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.***

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 central[63] and/or peripheral[16] 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 al[6] 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, respectively[18]; 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