THRESHOLD TRACKING FOR ASSESSMENT OF LONG-TERM ADAPTATION AND SENSITIZATION IN PAIN PERCEPTION [1]

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Summary.—To assess temporal variations in the perception of "phasic" heat pain stimuli a psychophysical tracking procedure was developed that enables repeated assessment of the pain threshold at short intervals. This "double-tracking" procedure produces two tracking curves simultaneously, one that approaches the pain threshold gradually from above, the other from below. The threshold for phasic heat pain was measured in 80 tracking trials with stimuli at temperatures near the pain threshold. Concurrently, the threshold for "tonic" heat pain was determined after every 20 tracking trials with a stimulus adjustment procedure. Eleven healthy subjects (age: 26.4 yr. ± 6.0) participated in 2 sessions each. Phasic stimulation near the pain threshold did not produce any trends in either of the two threshold measures. Hence there was no long-term adaptation or sensitization. However, there were random variations (random walks) in the tracking curves, which we interpret as resulting from a stochastic relationship between stimulus and sensation. In agreement with other reports, discrimination seemed to be better at painful than at nonpainful temperatures.

Tracking methods are an established tool in research on the psychophysics of auditory and visual perception (von Békésy, 1947). An element common to all such procedures is that stimulation is dependent on prior or concurrent responses of the subject in such a way that a psychophysical criterion, e.g., a threshold, is approached. In the study of somesthesia, however, such techniques have seldom been used (Dyck, Zimmermann, O'Brien, Ness, Caskey, Karnes, & Bushek, 1978; Jamal, Hansen, Weir, & Ballantyne, 1985; Kenshalo, 1986). To our knowledge, the pilot study of LaMotte and Campbell (1978) has been the only attempt in pain psychophysics. But tracking could be useful for studies of variation in the pain threshold over time, such as adaptation and sensitization, because it would enable ongoing measurement of the threshold over relatively long periods of time with only a small number of stimuli.

Variations in pain perception under conditions of repeated or continuous stimulation were reported early on (Dallenbach, 1939). The findings since then have been conflicting. Repeated electrical stimulation of tooth pulp led to adaptation of pain perception for stimulus intensities both markedly above and close to the threshold (Mumford, 1965; Ernst, Lee, Dworkin, & Zaretsky, 1986). In a study with a pressure algometer, however, Saumet (1984) found adaptation of pain perception for stimuli

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markedly above the threshold but no change for stimuli near the threshold. Green and Hardy (1962) reported only a slight change in pain perception for constant heat stimulation near the threshold, the trend being toward sensitization. In a study with repeated discrete stimulation at temperatures between 41°C and 43°C, Adriaensen, Gybels, Handwerker, & Van Hees (1984) found suppression of C-fiber activity and a reduction in pain sensitivity. In a study with 60 heat pain stimuli, some well above and some well below the pain threshold, a slight adaptation was produced (Lautenbacher, Möltner, Lehmann, Galfe, Hölzl, & Strian, 1989). Hence, adaptation or sensitization in the perception of pain may result from interactions among stimulation technique, stimulus intensity and psychophysical method.

In the present study a tracking procedure was used to investigate the variations in pain perception that occur under repeated application of painful heat stimuli. Because no suitable procedure was available for this purpose, a new procedure had to be developed. For this reason the tracking technique is described in detail.

The purpose of the study was twofold: (1) We wanted to determine whether long-term adaptation or sensitization occurs when phasic stimuli are used in the tracking procedure with temperatures very close to the pain threshold. As phasic pain stimuli (stimuli of not much more than one second in duration) and tonic pain stimuli (prolonged stimuli of at least several seconds in duration) may activate different sensorial and perceptual processes, e.g., differing degrees of central summation, we were interested in studying the effect of repeated phasic stimulation on the perception of both types of pain. (2) If one assumes a stochastic relationship between stimulus and sensation, as is postulated in signal-detection theory (McNicol, 1972), then random variations will be seen with any procedure used to track the pain threshold. For this reason we also investigated whether the tracking curves looked like random walks; we expected to find limits on the random walks because the location of the pain threshold is not arbitrary.

Method

Subjects

The subjects were 11 healthy adults (5 women and 6 men, mean age: 26.4 yr., *SD*: 6.0). The experiment was described to them and they were told that they could stop at any time. They were paid for participating.

Procedure

With one exception, the subjects participated in two sessions each. The procedure was the same in each session. It involves what we have termed "double tracking," with two independent tracking curves approaching each other from above ("pain") and below ("no-pain") the pain threshold.

Determination of starting points.—First, the stimulus intensities "pain" and "no pain" for the double-tracking procedure were selected. An approximation of these temperatures was made with a stimulus adjustment procedure that measures the threshold for tonic heat pain. This method involves constant stimulation for 30 sec. at the adjusted pain threshold temperature, followed by readjustment to compensate for initial response bias ["subjective sensitization" method; for a detailed description see Severin, Lehmann, and Strian (1985) and Lautenbacher, *et al.* (1989)]. Next, starting 0.5°C below the tonic pain threshold so determined, an ascending series of phasic stimuli such as is used in the tracking procedure was administered. Phasic stimuli at this initial temperature never elicited pain sensations. The temperature increment was 0.25°C; three stimuli were administered at each temperature. The series ended when all responses were "pain" for two successive temperatures. In the ascending series so determined the last but one temperature classified as "no pain" and the last classified as "pain" were taken as the starting points for double tracking.

Double-tracking procedure.—The procedure consisted of a series of 80 trials with a stimulus interval (10 sec.) and a response interval (20 sec., unless the subject responded sooner). In this series, the two types of stimuli, "pain" (above-threshold temperatures) and "no pain" (below-threshold temperatures), were always presented in pairs, but the order within each pair was random. This resulted in 40 trials for "pain" and 40 for "no pain." Table 1 shows the tracking algorithm. The steps up and down always refer to the next trial of a given tracking curve, that is, the tracking curves for "pain" and "no pain" varied independently of one another. The only restriction was that the two curves were not allowed to cross. If at any time they reached the same temperature, only tracking steps away from the threshold were possible.

The subjects got feedback on whether their response was correct, i.e., "pain" for above-threshold stimulation and "no pain" for below-threshold stimulation, or incorrect. As an additional incentive to use both perceptual categories, they also were paid DM 0.50 for each correct response. Care was taken in the instructions not to give any indication of what the criteria for a correct response might be.

The series of 80 trials with phasic stimuli was divided into four blocks of trials. Before and after each block the pain threshold for tonic heat stimulation was determined with the stimulus adjustment procedure. Prior to the first block there was a training phase in which the temperatures for "pain" and "no pain" were held constant. This training phase consisted of 10 to 20 trials. It ended when the subject had responded correctly eight times and had made no mistake on the last two trials. The end of the training phase (and the beginning of the tracking itself) was not signaled to the subjects.

According to the tracking algorithm, 80 phasic stimuli were administered all of which were near the pain threshold. With the design used the effects of this repeated stimulation could be monitored continuously with the tracking procedure (phasic pain threshold) and at intervals with the stimulus adjustment procedure (tonic pain threshold).

TABLE 1
ALGORITHM FOR DOUBLE TRACKING OF PAIN THRESHOLD
(S = STIMULUS, R = RESPONSE, i = CURRENT TRIAL, $i+1$ = NEXT TRIAL)

	Below-threshold		Above-threshold	
S_i	(No pain)		(Pain)	
R_i	Incorrect (Pain)	Correct (No pain)	Correct (Pain)	Incorrect (No pain)
S_{i+1}	2 Steps down − 0.5 °C	1 Step up + 0.25 °C	1 Step down − 0.25 °C	2 Steps up + 0.5 °C

Apparatus

Cutaneous heat stimuli were applied with a stimulator that had been developed in the Department of Neurology of the Max Planck Institute for Psychiatry. The device controls a Marstock thermode (for technical details see Fruhstorfer, Lindblom, & Schmidt, 1976) that functions on the Peltier principle and can be both heated and cooled. The temperature at the interface between the thermode and the skin was measured with a thermocouple (NiCr-Ni) and was registered continuously with a pen recorder (Philips PM8252). This was so the major stimulus parameters (amplitude, shape of leading edge, duration) could be monitored. The base temperature was 40°C and the rate of heating and cooling of the phasic stimuli 2°C/sec. The measuring voltage of the thermocouple was amplified and fed into a voltage comparator. When the stimulus amplitude specified on the voltage comparator was reached the temperature returned to the base value automatically, resulting in a phasic stimulus with a triangular form. This configuration allowed us to reproduce stimuli with a precision of 0.1°C.

The stimuli were administered and temperature measured on the thenar eminence of the right hand, with the subject's hand lying on a half sphere made of PVC. The thermode was mounted inside the half sphere and was held against the skin at a constant pressure by a spring. During the stimulus adjustment task ("subjective sensitization") the subjects regulated the temperature with a knurled wheel located in the half sphere within reach of their index finger. During the ascending series of stimuli the subjects gave verbal reports of "pain" and "no pain." In the tracking procedure they indicated that they had felt "pain" or "no pain" by pushing one of the two buttons. They received feedback on whether their response was correct or incorrect via two light-emitting diodes (green = "correct" and red = "incorrect").

Evaluation

Variations in pain perception during a session were evaluated separately for the tonic pain threshold (stimulus adjustment procedure) and the phasic pain threshold (tracking procedure). For the tonic pain threshold, the thresholds before and after each block were averaged, yielding four means from the five thresholds. These threshold measures were then tested for ascending or descending monotonic trends with the *L* test, a nonparametric test for increases or decreases in the rank sums calculated by the Friedman test (Page, 1963). For the phasic threshold, the first step was to compute a "middle tracking curve." This was done by averaging the paired values (in each case one value from the above-threshold curve and one from the below-threshold curve). The middle tracking curve obtained for each session thus included 40 data points. A within-block mean was then calculated for each block, yielding four values representing periods of time similar to those for the tonic pain threshold measures. Again, the four threshold measures for each session were subjected to the *L* test.

Next, to identify any marked upward or downward variations in each of the 21 middle tracking curves (excluding short-term variations), the line of regression for threshold temperature and pair number was calculated for each block. If the slope of the regression line indicated a change of $>0.5°C$ or $<-0.5°C$ within a block, then an "UP" or "DOWN" variation, respectively, was scored. Smaller variations were classified as "NO" variation. The frequency distributions of "UP," "DOWN" and "NO" variation were then analyzed within and between blocks as well as over-all by the chi-squared test.

To test the hypothesis that tracking curves behave like random walks, the autocorrelation function of the first differences was calculated for each middle tracking curve. The lags ranged from 0 to 12. The distribution of positive and negative correlation coefficients per lag in the group was determined and tested for a difference from a zero correlation (binomial test).

RESULTS

Fig. 1 shows the results of the trend analysis for both the tonic pain threshold (stimulus adjustment procedure) and the phasic pain threshold (tracking procedure). The tonic pain threshold increased from Block 1 to Block 4 by slightly more than 0.1°C and so was relatively stable. In contrast, the phasic pain threshold decreased by 0.3°C; in Block 4 it was only slightly above the tonic pain threshold. However, in the *L* test both changes were classified as nonsignificant trends (phasic threshold: $p = .313$ for the descending trend, tonic threshold: $p = .287$ for the ascending trend).

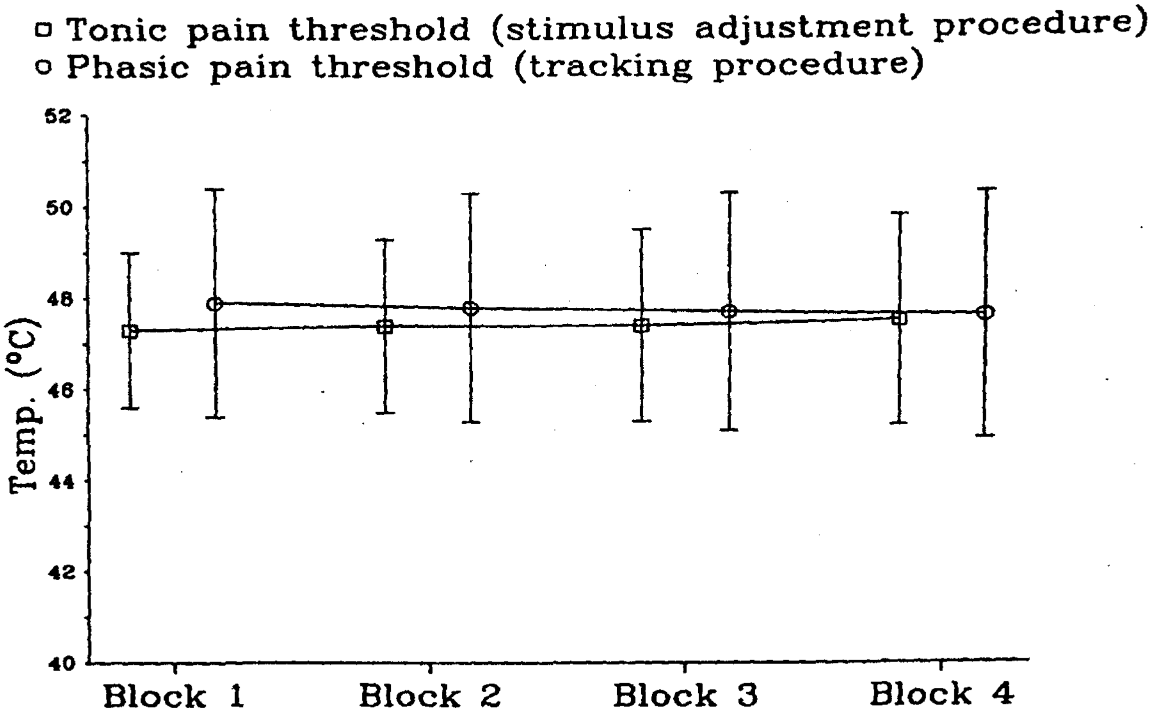

FIG. 1. Mean pain thresholds (with *SD*) under tonic stimulation (stimulus adjustment procedure) and phasic stimulation (tracking procedure) in each of the four blocks of trials ($n = 21$)

The assessment of variations in the middle tracking curve per block via linear regressions yielded the frequencies shown in Fig. 2. Sections with no variation or only a small variation (NO) were most frequent and significantly more frequent than "UP" or "DOWN" variations (NO vs UP and NO vs DOWN, $p < .001$). Downward variations were more frequent than upward variations (DOWN vs UP, $p = .041$), but both were relatively rare. The frequencies of "NO", "UP", "DOWN" variations did not differ between blocks (test for differences between blocks: NO $p = .881$, UP $p = .438$, DOWN $p = .560$).

The slightly greater frequency of downward variations explains the small decrease in the phasic pain threshold from Block 1 to 4 (see Fig. 1).

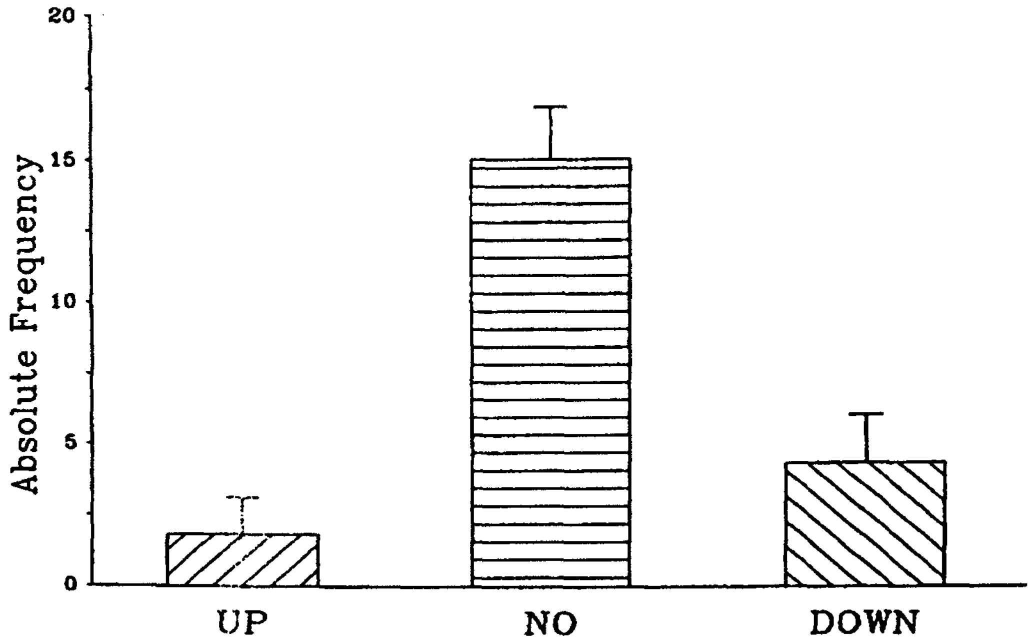

FIG. 2. Mean frequency of large variations (>0.5 °C) (with *SD*) in the tracking curves per block of trials; UP = increase, NO = no change, DOWN = decrease ($n = 21$)

This may be due to the greater frequency of correct responses for above-threshold stimuli (tracking curve "pain") than for below-threshold stimuli (tracking curve "no pain"). With these frequencies the tracking algorithm

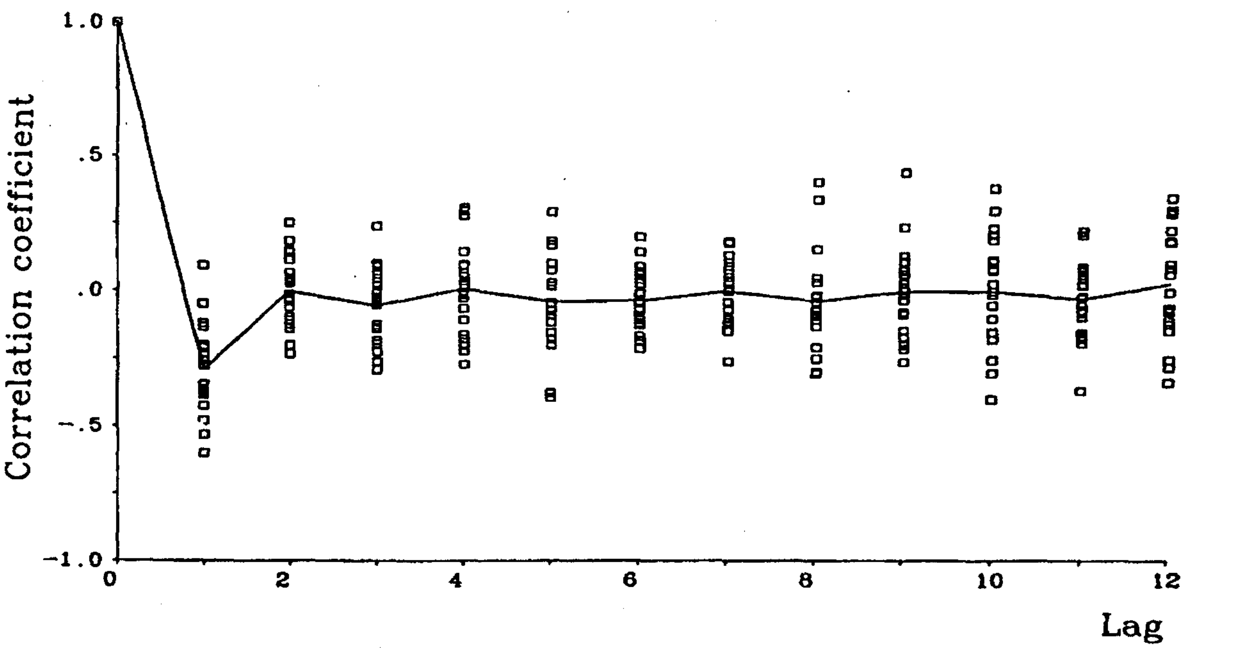

FIG. 3. Individual (squares) and mean (solid line) correlation coefficients for the autocorrelation functions for the first differences of the middle tracking curves from lag 0 to 12; mean correlation coefficients calculated via Fisher's r to Z transformation; one lag corresponds to a shift of one value in a series of values of the first differences ($n = 21$)

used makes a decrease in the middle tracking curve most likely. However, the hit rates of 72.3% and 69.3%, respectively, are not significantly different (chi-squared, $p = .31$).

Calculation of the autocorrelation functions for the first differences of the middle tracking curves was performed to find out whether there were any systematic variations in the curves or whether the curves behaved like random walks. Theoretically in a simple random walk the autocorrelation coefficients should be zero for lags which are greater than 0. Fig. 3 shows the coefficients.

There were no systematic clusters of positive or negative correlations on any of the lags except lag 1 (for a difference from a zero correlation, lag 1: $p < .001$; all other lags: $p > .05$). This suggests that there are no systematic variations in the tracking curves for the group as a whole. Hence the observed variations do indeed appear to be random, and this is an indication that the tracking curves exhibit random walk behavior. The cluster of negative correlations on lag 1 suggests that when the middle tracking curve shows an increase a decrease is more likely to follow and vice versa. This would not be expected for a simple random walk. Restrictions are necessary here such as those expected with a random walk with central restoring tendency (Cox & Miller, 1965).

Discussion

The present study investigated the phasic pain threshold over a relatively long period of time with a tracking procedure. A "double tracking" procedure was developed for this purpose which "guides" stimulus intensities in both the "pain" and "no pain" range toward the pain threshold. To prevent any response bias, a training phase and explicit consequences for the subjects' responses were included. Under these conditions the variations in the tracking curves should result primarily from adaptation or sensitization produced by repeated heat pain stimulation. A further hypothesis was that the tracking curves would behave like random walks even if the threshold level remained stable because of underlying stochastic relationships between stimulus and sensation.

No marked effects of the repeated application of pain stimuli could be demonstrated for either the phasic or the tonic threshold, i.e., long-term adaptation or sensitization did not result from phasic stimulation near the pain threshold. In conflict with these results, other studies have reported an adaptation of pain perception under similar stimulation conditions (Adriaensen, *et al.*, 1984; Lautenbacher, *et al.*, 1989). Factors important for adaptation or sensitization under conditions of intermittent heat pain stimulation are the intensity of previous stimuli and the intertrial interval (LaMotte, 1979). The differences between the studies cannot be explained by differences in the intertrial interval because the intervals were all in the range where a suppression of pain sensation is to be expected (less than 5 min.). Therefore, the intensity of previous stimulation is the more likely cause. In the study by Adriaensen, *et al.* the stimulus intensities were between 41°C and 43°C and consequently in a temperature range where usually weak pain sensations only are elicited. In the earlier study by our group (Lautenbacher, *et al.*, 1989) the stimulus intensities varied widely around the individual pain threshold, i.e., some of the stimuli administered were clearly above or clearly below the pain threshold. The tracking procedure in the present study led to a constant reduction in the difference between the stimulus intensity and the pain threshold. The results of these studies with intermittent cutaneous heat stimulation suggest that, if the intertrial interval is relatively short, stimulus intensities below or markedly above the pain threshold (defined as the 50%-point) produce adaptation, whereas stimulus intensities very close to the threshold do not produce any variation in pain perception.

If we also consider the findings under constant stimulation (Green & Hardy, 1962; LaMotte, 1979; Saumet, 1984; Severin, *et al.*, 1985), the following conclusion about the role played by the intensity of previous stimulation seems justified: pain stimuli that are close to the pain threshold or slightly above it lead either to no variation or to a slight increase (sensitization) in pain perception, whereas stimuli that are below or markedly above the threshold result in adaptation. In studies where tooth pulp was stimulated electrically this was not found, however (Mumford, 1965; Ernst, *et al.*, 1986). Here stimuli near or markedly above the threshold led to adaptation of pain perception. Whether these findings are in fact contradictory or are an indication of differences in peripheral transduction of cutaneous and dental stimuli is unclear at present.

There were no indications of any systematic variations in the tracking curves. All variations seen could be classified as random. Hence as hypothesized, the tracking curves behaved like random walks. The stochastic relationship between stimulus and sensation postulated in signal-detection theory (McNicol, 1972) also influences tracking of the pain threshold. All that was systematic was that if the tracking curve showed an increase then a decrease immediately thereafter was more likely and vice versa. We conclude that there are limits to the random walk and that it is probably a variant of a random walk with central restoring tendency (Cox & Miller, 1965). This is to be expected in any attempt to track the pain threshold because the location of the pain threshold is not arbitrary even if we assume stochastic stimulus-sensation relationships.

The slight but not significant downward trend in the tracking curves may be the result of somewhat better discrimination above than below the pain threshold. Corresponding, though also not significant, differences in the hit rates were found and with the tracking algorithm used they make a decrease in the tracking curves likely. The findings of LaMotte and Campbell (1978) that the psychophysical function had a steeper slope for the relationship between subjective intensity and temperature for painful than for nonpainful temperatures supports this notion. Further evidence is provided by studies in which perception of temperature differences is better at painful levels (47°C) or at least at relatively high temperatures (>40°C) than for temperatures below 40°C (Bushnell, Taylor, Duncan, & Dubner, 1983; Robinson, Torebjoerk, & LaMotte, 1983; Handwerker, Keck, & Neermann, 1982). According to this view, the slight drop in the tracking curves is not even a weak sign of a change in pain perception in the sense of adaptation or sensitization; rather it is the result of the psychophysical function in the transition area between heat perception and pain perception.

As the study shows, tracking procedures can provide new insights into the causes of temporal variations of pain perception, especially if one keeps their characteristics, i.e., the random walk behavior of the resulting curves, in mind. By modifying the tracking algorithm other conditions of repeated pain stimulation (e.g., more stimuli above or more below the threshold) can be produced easily and used in the study of adaptation and sensitization.

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