Diurnal variations in pain perception and thermal sensitivity

F. Strian, S. Lautenbacher, G. Galfe and R. Hölzl *

*Max Planck Institute for Psychiatry, Department of Neurology and * Department of Psychology, Munich (F.R.G.)*

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Summary Pain and thermal sensitivity thresholds in healthy volunteers were examined for diurnal variations. The subjects were 11 men aged between 22 and 27 years ($\bar{x}$ = 23.5, S.D. = 1.5). Data were collected for 2 days, with 7 measurements per day. To ensure the pain specificity of the results the subliminal modality, i.e., thermal sensitivity thresholds to warm and cold stimuli, was investigated in addition to the threshold for perception of heat pain. Assessments were made on the right hand and foot, the stimuli being presented with a thermoelectric contact-thermode. Despite the influence of variables other than time of day (45–56% of the total variance), diurnal variations were found for some subjects on the pain threshold measure (significant correlation between days and relatively high frequency of 24 h component in Fourier analysis spectra). However, they could not be demonstrated for the thermal sensitivity measures. The diurnal variations in pain perception thresholds did not have a consistent pattern over all subjects (Friedman test). The small diurnal variations with interindividual differences in the pattern are therefore not sufficient to explain the variations seen in clinical pain, but they may be useful in detecting pain modulators by investigating correlations.

Key words: Thermal sensitivity; Diurnal variations; Heat pain

Introduction

Cyclic variations in experiencing pain (circadian and circamensual fluctuations, etc.) have been known for a long time in the clinical context. They have been observed, for example, in patients with duodenal ulcers, migraine and tension headaches, toothache, and arthritis. Nevertheless, systematic studies that endeavor to determine the temporal pattern of these variations are still very rare and for most illnesses the results have been inconsistent [see 13 for a review]. Diurnal variations may be due to the primary noxious events, to the nociceptive system itself, or to a combination of both. In the case of duodenal ulcers, for example, the underlying mechanisms are variations in the quality of the mucous membrane and in the amount of acid secreted [15]. The protective function of pain makes dramatic diurnal fluctuations in the nociceptive system unlikely. However, pain perception is affected by many different factors which themselves exhibit diurnal variations, and this too may result in small diurnal variations. In this context, vegetative and hormonal variables as well as psychological state factors should also be kept in mind [6,8,11,14].

If the existence of cyclic variations in pain perception in healthy persons could be established, this would help us to understand better both what factors can cause diurnal variations and whether these are adequate to explain the variations seen in clinical pain. Past psychophysical studies on temporal variations in pain perception (in particular circadian and circamensual fluctuations) in healthy persons have not yielded a uni-

Correspondence to: Dr. Friedrich Strian, Max-Planck-Institut für Psychiatrie, Neurologische Poliklinik, Kraepelinstr. 10, 8000 Munich 40, F.R.G.

form picture. This can be explained in part by the methods applied: often the sampling rates (number of measurements per unit of time) and type of stimulation (e.g., electric or thermal) were not comparable [7,8,14]. Nevertheless, diurnal variations of clinical relevance should be detectable despite differences in method.

The objective of the present study was to address the controversial issue of whether there are diurnal variations in pain perception in healthy persons. The hypothesis tested was that diurnal variations are present in such individuals but that they are only minimal and are, therefore, neither test- nor method-invariant. Large variations with a consistent pattern within a group of subjects should give rise to statistically significant differences in means between measuring points. Smaller variations or differences in time course should be detectable if tests with fewer prerequisites are used. We, therefore, examined our data with several different statistical tests with different prerequisites. Furthermore, we addressed 2 problems that have not received enough consideration in the past: Firstly, the detection of cyclic variations is complicated by the large interindividual differences and the unsystematic fluctuation occurring intraindividually. In the present study we determined the proportion of the variance due to the factors just mentioned and separated it from the relevant diurnal variations. Secondly, variations that are assumed to be pain specific may actually be caused by more general changes in perception. Here it is particularly important to consider the subliminal sensory modality for the same physical dimension. We therefore assessed sensitivity to warm and cold stimuli in addition to heat pain thresholds.

Method

Subjects

Eleven men aged between 22 and 27 years ($\bar{x} = 23.5$, S.D. = 1.5) participated in the study. We decided not to study women to avoid the overlap of daily and monthly variations. Potential subjects were excluded from the study if it became evident in an interview that they were suffering from any illness or taking medicine that might influence pain and temperature perception.

TABLE I

OVERVIEW OF THE THRESHOLDS ASSESSED (DEPENDENT VARIABLES)

Thermal sensitivity	Warmth threshold hand	(WTH)
	Warmth threshold foot	(WTF)
	Cold threshold hand	(CTH)
	Cold threshold foot	(CTF)
Pain perception	Pain threshold hand	(PTH)
	Pain threshold foot	(PTF)

Procedures and apparatus

Data were collected for 2 days with 7 measurements per day at the following times: 7.00, 10.00, 13.00, 16.00, 19.00, 22.00, 2.30. Each sequence began at 7.00. The dependent variables were sensitivity to warmth and cold and perception of heat pain. The stimuli were applied to the right hand and foot (see Table I).

The thermal stimuli were produced with a modified Marstock thermode [4]. The thermode functions on the basis of the Peltier effect. Depending on the direction of the flow of current through the element, the contact surface heats or cools. The heating and cooling speed can be regulated with the thermode control via the current intensity. In the present study the speed was between 0.5 and 1.0 °C/sec, depending on the intensity of the stimulus. The contact surface was 2×3 cm. The water flowing along the opposing side of the thermode was 30 °C and stabilized the baseline temperature in the interstimulus interval. The point of stimulus on the *hand* was the thenar. The subject placed his hand on the curved surface of a half sphere made of hard PVC under which the thermode had been installed. The point of stimulus on the *foot* was the dorsum. In this case, the thermode was applied with a swivel arm. During the experiment the subject sat in a comfortable armchair. In each trial, when he perceived that the threshold had been reached, he had to press a response key. This reversed the flow of current, and the thermode was then actively cooled or heated to the baseline temperature. The threshold

temperature was defined as the value on the temperature curve at the point of reversal.

To determine the *warmth and cold thresholds* (WTH, WTF, CTH, CTF) a series of 5 warm and 5 cold stimuli were administered in a randomized order. As soon as the subject perceived a change in temperature, he was to press the response key. In the case of 'incorrect' reactions (e.g., incorrect attribution of quality), the trial was repeated. The threshold measure was the difference between the baseline temperature and the threshold temperature.

To determine the *pain thresholds* (PTH, PTF), 5 thermal stimuli were administered in a second run. As soon as the subject perceived pain, he was to press the response key. The threshold measure was the threshold temperature itself.

Because this kind of discriminatory performance does not become stable until after several trials [16], the means used in the subsequent data analysis were calculated from the 4th and 5th trials only.

Data analysis

The statistical analysis was divided into 3 steps in accordance with the theoretical points of emphasis (see Introduction).

Step 1: assessment of unsystematic variance. To assess overall differences in thresholds between day 1 and day 2, the Wilcoxon signed rank test was applied. To determine the reliability of thresholds Pearson coefficients of correlation were calculated for measurements obtained at the same time of day but on different days. This was done in 2 ways, with method A separately for each time of day (7 correlations) and with method B for all times combined (1 correlation). To obtain an overall reliability value from method A, a mean correlation coefficient was then calculated from the 7 coefficients using a Fisher z transformation.

Step 2: examination for intraindividual diurnal variations. Intraindividual uniformity in the pattern of the values on the 2 days was assessed by calculating the Pearson coefficients of correlations after z transformation of the values (standard z per day and subject). The correlation between the pairs of z values for the 2 days was then calculated according to method B (see step 1). This calculation permits statements about the mean degree of similarity in intraindividual variations between days, but not about their individual temporal pattern. Therefore the 2 day sequence of data for each subject was additionally subjected to a Fourier analysis [see 3 for the rationale for using the Fourier analysis in chronobiology]. To compensate for the non-equidistant sequence of values, the 14 data points (7/day) were increased to 88 (2/h) by interpolation. The evaluation of the spectra was limited to the frequency range of 1/24 h, with the 24 h component falling in the period of 1320 ± 414 min. Two parameters were determined: (a) the existence of a peak with 30% or more of the total power of the spectrum, and (b) the time interval (7.00–14.59, 15.00–22.59, 23.00–6.59) in which the cycle minimum lay (interval selection was made with reference to sleeping and measurement times). Frequency statistics were calculated on the basis of these parameters. To check for random results, normally distributed random numbers (also 14 data points/sequence) were subjected to the same procedure in 10 simulation experiments. The frequency distribution of the parameters from the simulations was then compared with the observed data.

Step 3: examination for interindividual similarities in diurnal variations. The question of the extent to which any diurnal variations seen in individuals showed interindividual similarities was answered using the Friedman test to check for differences between the measurement times for the pooled values from all subjects and both days.

Results

Step 1: assessment of unsystematic variance

Table II shows that there was a difference between days 1 and 2 for the warmth thresholds (WTH, WTF) only. However, even here the difference was not significant ($P > 0.05$).

Table III shows the correlation coefficients for reliability for measurements made at the same time of day but on different days. Calculation method A (see section on data analysis) yielded correlation coefficients that are all slightly higher than those obtained with method B. Method A

TABLE II

MEANS ($\bar{x}$) WITH STANDARD DEVIATION (S.D.) FOR THE THERMAL SENSITIVITY MEASURES AND THE PAIN THRESHOLD MEASURES ON DAYS 1 AND 2 FOR ALL MEASUREMENT TIMES

The number of values (n) included and the P values for the Wilcoxon signed rank test for differences between the 2 days are also given.

Variable	Day 1 ($\bar{x} \pm$ S.D.)	Day 2 ($\bar{x} \pm$ S.D.)	P	n
Thermal sensitivity				
WTH	1.92 ± 1.23	1.68 ± 0.89	0.09	77
WTF	3.85 ± 2.62	3.53 ± 2.56	0.07	75
CTH	1.14 ± 0.54	1.18 ± 0.46	0.25	77
CTF	1.98 ± 1.21	1.98 ± 1.43	0.32	76
Pain perception				
PTH	47.88 ± 2.63	47.96 ± 2.39	0.20	76
PTF	46.40 ± 2.59	46.50 ± 2.23	0.20	75

provides the better estimate of reliability because it takes into consideration the distribution of the covariates for each time of day. Because the mean correlations were never higher than 0.74, this is an indication that there was considerable unsystematic variation in all threshold variables. The calculation of the coefficients of determination (r^2) shows that this kind of variance contributes between 45% (WTH) and 56% (PTF) of the total variance. Thus variables other than time of day clearly influence the measurements and increase the difficulty of detecting any cyclic variations.

TABLE III

PEARSON CORRELATION COEFFICIENTS (r) FOR THE CORRELATION BETWEEN DAYS 1 AND 2 FOR THE THERMAL SENSITIVITY MEASURES AND THE PAIN THRESHOLD MEASURES

Columns 1 and 2: based on raw values, column 1 calculated by method A, with the range of the individual correlations also given; column 2 calculated by method B (see the section on data analysis); column 3: based on z values; column 4: P values for the correlations in column 3; column 5: the number of values included (n).

Variable	Raw values			z values		
	(1)		(2)	(3)	(4)	(5)
	r	(range)	r	r	P	n
Thermal sensitivity						
WTH	0.74	(0.52–0.85)	0.55	0.02	0.44	77
WTF	0.68	(0.51–0.85)	0.60	−0.09	0.23	75
CTH	0.73	(0.50–0.90)	0.71	0.00	0.50	77
CTF	0.71	(0.05–0.92)	0.68	0.10	0.19	76
Pain perception						
PTH	0.69	(0.33–0.81)	0.63	0.28	< 0.01	76
PTF	0.66	(0.29–0.84)	0.62	0.25	0.01	75

Step 2: examination for intraindividual diurnal variations

Table III also shows the Pearson coefficients of correlation based on z values for days 1 and 2 (see section on data analysis). Because the z transformations eliminate the contribution of the interindividual variance (differences in mean threshold level), the intraindividual covariance between days in the group becomes evident with this calculation. For the thermal sensitivity measures no covariation was found between days 1 and 2. Thus no similar intraindividual diurnal variations between days could be demonstrated. The low but nevertheless significant correlations for the pain threshold measures support the hypothesis of similar intraindividual variations on days 1 and 2. The results presented so far in step 2 show the strength of the intraindividual covariations on the 2 days throughout the entire group; but they provide little information about the strength and phase position of the 24 h periodicity in each subject.

The highest percentage of spectra with a marked 24 h component ($\geq 30\%$ of the total power) was found for the pain threshold measures (Table IV). This finding differs significantly from the results obtained with random sequences (see section on data analysis). Regarding the 4 thermal sensitivity measures, this is true only for the cold thresholds determined on the foot. Nevertheless, the differences between the thermal sensitivity and pain threshold measures were too slight to permit classification of the variations found as clearly specific to pain. After all, in 50% of the frequency spectra, 24 h periodicity could not be demonstrated even for the pain thresholds. This result together with the relatively low correlations throughout the entire group indicate that substantial diurnal variations in pain perception do exist, but not in all people. Because the results obtained so far did not demonstrate any diurnal variations in sensitivity

TABLE IV

NUMBER AND PERCENTAGE OF FREQUENCY SPECTRA WITH A MARKED 24 h COMPONENT (for assessment of spectra see the section on data analysis) ON THE THERMAL SENSITIVITY MEASURES AND THE PAIN THRESHOLD MEASURES, WITH LINE AND COLUMN TOTALS

In addition, the probability is given (* < 0.05 and ** < 0.01) of obtaining the same percentages when random sequences are analyzed (see the section on data analysis).

	Hand	Foot	Total
Warmth	4	4	8
threshold	36.4%	36.4%	36.4%
Cold	3	6 **	9 *
threshold	27.3%	54.5%	41.0%
Pain	5 *	6 **	11 **
threshold	45.5%	54.5%	50.0%
Total	12	16 **	28 **
	36.4%	48.5%	42.4%

to temperature, each subject's times of lowered thresholds were determined from the spectra for the pain thresholds only.

Fig. 1 shows that when there was a marked 24 h component the pain threshold tended to be lower, i.e., there was increased sensitivity to pain, in the afternoon and evening hours (15.00–22.59). However, for 45.5% of the spectra included, the lowest pain threshold was not within this time period.

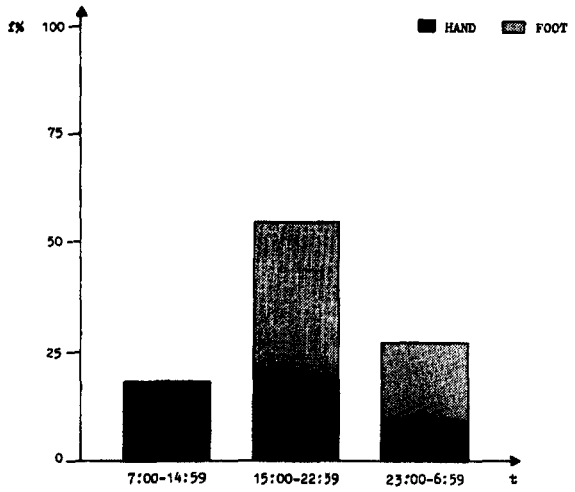

Fig. 1. For the pain threshold measures, percentage of the frequency spectra in which the lowest threshold value (determined by the phase position in the frequency spectra) occurred in a given time interval. Only those spectra with a marked 24 h component (n = 11) are included.

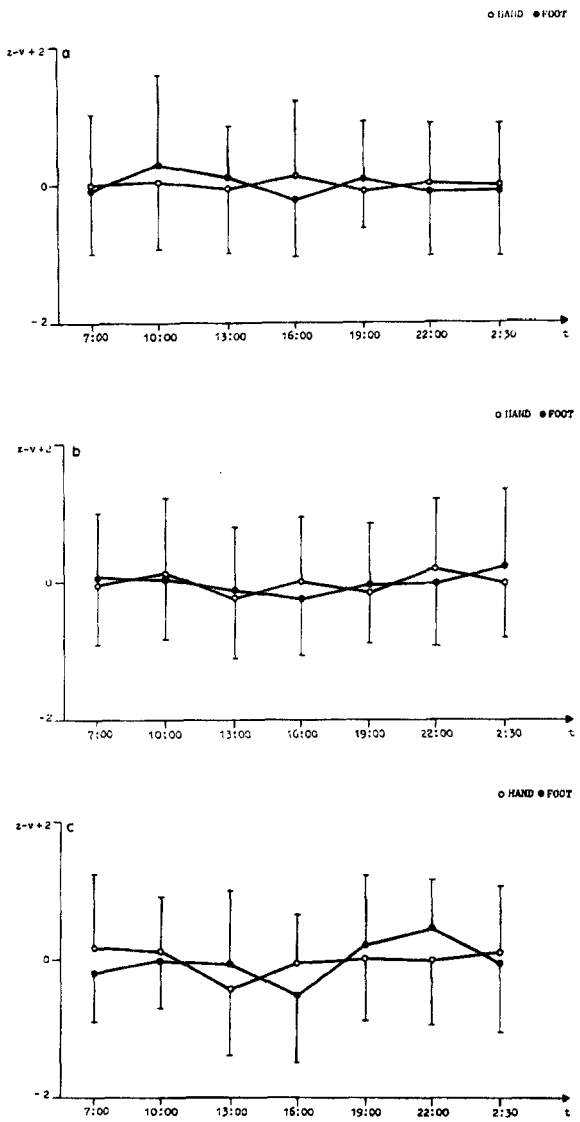

Fig. 2. Means and standard deviations of the pooled z values (transformed per day and subject) for the 7 measurement times and both days. a: sensitivity to warmth (WTH, WTF); n = 22, except for WTF 7.00 and 10.00, where n = 21. b: sensitivity to cold (CTH, CTF); n = 22, except for CTF 13.00, where n = 21. c: perception of pain (PTH, PTF); n = 22, except for PTH 16.00 and PTF 7.00 and 13.00, where n = 21.

Step 3: examination for interindividual similarities in diurnal variations

The means of the pooled z-transformed values from days 1 and 2 for the 7 data points are shown in Fig. 2a, b and c.

The use of z values facilitates demonstration of diurnal variations in the group by eliminating the contribution of the interindividual variation. No significant differences in the values for the different times of day were found for any of the threshold measures (Friedman test, WTH: $P = 0.979$, WTF: $P = 0.355$, CTH: $P = 0.931$, CTF: $P = 0.666$, PTH: $P = 0.545$, PTF: $P = 0.151$). Thus even the daily fluctuations in the pain threshold measures found in some subjects (see Results, step 2) were too slight and/or too variable to produce significant effects for the group as a whole.

Discussion

Distinct diurnal variations with interindividual similarities in form could be demonstrated neither for sensitivity to temperature (perception of warmth and cold) nor for perception of pain. Therefore, the results from this and similar studies can provide only partial explanations for the sometimes drastic variations seen in clinical pain in the course of a day [13]. No conclusions on time-dependent use of analgesic drugs can be drawn from these studies [5].

With regard to slight diurnal variations with interindividual differences in form, our findings for thermal sensitivity thresholds were different from those for pain thresholds. In the case of thermal sensitivity we found an almost complete lack of any indication of systematic fluctuations. On the pain threshold measures some of our subjects exhibited a daily rhythm; the variations were only slight, however, and the temporal relations were relatively inconsistent. The variations were small enough that they would not affect the protective function of pain. It seems likely that they can be attributed to fluctuations in such things as activity, the sleep–wake rhythm and nutritional habits, all of which have inconsistent diurnal patterns under non-standardized conditions.

Our results therefore support the approach in pain research of trying to identify pain modulators by looking for diurnal covariation with other variables. Experiments of this kind have already been conducted, for example, on endorphin metabolism [2,12] and mood variables [11]. For this purpose, small variations are sufficient. The variations must be pain-specific, however. A parallel comparison of supraliminal and subliminal perception modalities such as was undertaken in the study reported here is necessary to ensure the validity of the results.

From this point of view, the examination of diurnal variations can be considered worthwhile despite the lack of interindividual similarities and dramatic fluctuations. However, as we were able to show, the strong influence of variables other than time of day complicates the process of detecting small diurnal variations. This was not taken into consideration sufficiently in past studies on the subject. Further improvements in strategies for detection are therefore necessary. This includes, among other things, parallel comparisons of different types of pain [e.g., 7] and experimental designs with more frequent assessments within a given time period and/or longer observation intervals, which would allow time-series analysis. If the latter point is taken into account, then very weak periodicities could be detected with Fourier analysis or similar methods. Seven data points per day for 2 days probably represent the lower limit.

On the whole, our results are consistent with those reported in the literature. We found diurnal variations that are probably specific to pain, but we could not demonstrate this unequivocally. Because clear diurnal variations with interindividual similarities in form apparently do not occur in pain perception, it is not suprising that some studies have yielded positive results and others negative ones [1,2,6,8–12,14]. The demonstration of slight diurnal variations with no consistent pattern depends largely on the approach of the study and the tests used, as we were able to show. Similar limitations apply for the chronological position of the diurnal variations. The existence of a period of time with increased pain sensitivity between 15.00 and 22.59 (see Results) is compatible with the increased pain sensitivity in the

afternoon and/or evening found by several other authors [1,2,10,11]. In this case, as in others, conclusive results can be achieved only if improved methods of examination are used.

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