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Percentile normative values of parameters of electrical pain and reflex thresholds

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HIGHLIGHTS

- Descriptive statistics of electrical reflex and pain thresholds in large samples are known.
- This study provides estimates of percentile normative values for these assessments.
- These values can be used to assess widespread hyper- and hyposensitivity in individual patients.
- These values can also be used in future research on mechanism-based treatment of chronic pain.

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ABSTRACT

Background and purpose: Central hypersensitivity, defined as an increased excitability of the central nervous system, is considered as the main factor behind facilitation of central pain processes and is probably a very important factor in the induction and maintenance of chronic pain. Widespread hyposensitivity is less studied than hypersensitivity states, but recent work indicates that hypoesthesia may be present in chronic non-neuropathic pain conditions and could have negative prognostic value. Electrical pain and reflex thresholds are well established measures of central pain sensitivity in human pain research. One potential application of these assessments in clinical practice is the detection of central hyper- or hyposensitivity in individual patients. In order to identify these disturbances in the central pain processing of individual patients, knowledge of reference values is essential. We computed percentile normative values of nociceptive withdrawal reflex (NWR) and pain thresholds to different electrical stimulation paradigms. The aim was to provide reference values for the assessment of widespread central hyper- and hyposensitivity in individual patients.

Methods: 300 pain-free subjects (150 males and 150 females, 18–80 years) were studied. Pain and reflex thresholds to single and repeated electrical stimulation (applied on the innervations area of the sural nerve), and the area of reflex receptive fields (RRF) were recorded. The RRF area was defined as the skin area of the sole of the foot from which a NWR could be evoked in the tibialis anterior muscle, expressed as proportion of the foot sole. For the threshold assessments, quantile regressions were performed to compute critical normative values for widespread central hypersensitivity (5th, 10th and 25th percentiles) and hyposensitivity (75th, 90th and 95th percentiles). For the RRF the opposite applied, computing normative values for widespread central hypersensitivity as 75th, 90th and 95th percentiles, and normative values for hyposensitivity as 5th, 10th and 25th percentiles. The following covariates were included in the regression analyses: gender, age, height, weight, body mass index, body side of testing, depression (Beck Depression Inventory), anxiety (State-Trait-Anxiety-Inventory), catastrophizing (Catastrophizing Scale of the Coping Strategies Questionnaire) and Short-Form 36.

Results: Age had a significant impact on the subjective pain threshold to single electrical stimuli. The reflex threshold to single electrical stimuli was lower on the dominant compared to the non-dominant side. Therefore, the percentiles for single stimulus pain threshold have been stratified by age and

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the percentiles for single stimulus reflex threshold by body side (dominant *vs.* non-dominant). Critical normative values of all tests were computed for widespread central hypersensitivity (5th, 10th and 25th percentiles) and hyposensitivity (75th, 90th and 95th percentiles). The values are provided in the table of the manuscript.

Conclusions and implications: The computed estimates of critical normative values for the electrical pain test can be used in clinical practice for the assessment of widespread central hypersensitivity and hyposensitivity in individual patients, and in future research on mechanism-based treatment of chronic pain.

1. Introduction

Central hypersensitivity, defined as an increased excitability of the central nervous system, is considered as the main factor behind facilitation of central pain processes and is probably a very important factor in the induction and maintenance of chronic pain [1]. Widespread hyposensitivity is less studied than hypersensitivity states, but recent work indicates that hypoesthesia may be present in chronic non-neuropathic pain conditions and could have negative prognostic value [2].

Central sensory disturbances have been detected by various modalities of experimental pain tests in different chronic pain states not necessarily associated with neuropathy [3–7]. Electrical pain and reflex thresholds are well established measures of central pain sensitivity in human pain research [8,9]. In a recent investigation that ranked different assessments of pain sensitivity according to their ability to discriminate between patients with low back pain and pain-free controls, electrical pain tests were among the ones with the best performance [10].

One potential application of these assessments in clinical practice is the detection of central hyper- or hyposensitivity in individual patients. This would provide information on the pathophysiological mechanisms underlying the patient's symptoms and may guide treatment decisions. In order to identify these disturbances in the central pain processing of individual patients, knowledge of reference values is essential.

In a previous investigation conducted on 300 pain-free volunteers [11], we presented summary statistics and a multifactorial analysis for spinal nociceptive withdrawal reflexes (NWR), subjective pain thresholds to single and repeated electrical stimulation, and area of the reflex receptive fields (RRF). An important limitation of that study is the lack of estimation of critical values for the pain tests that would allow the identification of potential hyper- or hypoexcitability states in patients.

In the present investigation, we analyzed the sample of the previous investigation [11] to estimate critical normative values for each pain test. The aim was to provide estimates of percentile normative values of these tests that can be used for assessing widespread central hyperexcitability and hyposensitivity in individual patients.

2. Methods

The present study is based on the sample analyzed in the aforementioned previous investigation. The selection of the sample, the description of the variables, and an explanation of the pain tests are presented in detail in that study.

2.1. Participants

The study protocol was approved by the ethics committee of the University of Bern (KEK 147/04) and was in accordance with the Declaration of Helsinki. 300 pain-free subjects (150 males and 150 females, 18–80 years old) were studied. Exclusion criteria were: no knowledge of German language, any acute or chronic pain condition, intake of any pain medication for less that 24 h before the investigation, pregnancy (as ruled out by pregnancy test in women in reproductive age) and breast feeding. Participant selection was made so that 75 subjects were analyzed within each of the following age categories: 20–34, 35–49, 50–64 and 65–80 years. Furthermore, the male: female ratio within each age category had to be 1:1 (±1). All volunteers provided written informed consent before participating.

Gender, age, height, weight and body mass index (BMI) were recorded. Then the volunteers were asked to fill four questionnaires: Beck Depression Inventory (BDI), State-Trait-Anxiety-Inventory (STAI), Catastrophizing Scale of the Coping Strategies Questionnaire and Short-Form 36 (SF-36).

2.2. Pain tests

2.2.1. General aspects

All the experiments were performed by the same investigator (AN). Each subject underwent a training session for all tests in order to get familiar with the stimulation procedures before starting the data collection. Single electrical stimulation, repeated electrical stimulation (temporal summation) and test for reflex receptive field were performed in a randomized order. All the tests were applied to the same body side within each subject, the side being selected randomly.

2.2.2. Thresholds to single electrical stimulation

Electrical stimulation was performed through surface electrodes placed caudal to the lateral malleolus, at the innervation area of the sural nerve [12]. A 25 ms train-of-five square-wave impulses, each lasting 1 ms, was delivered by a computer-controlled constant current stimulator (University of Aalborg, Denmark). The stimulation train is perceived as a single stimulus. Electromyographic (EMG) reflex responses to electrical stimulation were recorded from the middle of the biceps femoris and the rectus femoris muscles (Ag/AgCl-electrodes).

The current intensity was increased from 1 mA in steps of 0.5 mA until: (1) a reflex with an amplitude exceeding 20 μV for at least 10 ms in the 70–150 ms post-stimulation interval was detected (single stimulus reflex threshold); and (2) a pain sensation was evoked (single stimulus pain threshold). The program delivered the impulses at random time intervals (between 8 and 12 s), so that the subject was not aware of when the stimulus was applied.

2.2.3. Thresholds to repeated electrical stimulation (temporal summation)

The stimulus burst used for single stimulus was repeated five times with a frequency of 2 Hz, at constant intensity [13]. EMG recordings were similar as for single stimulation. The current intensity of the five constant stimuli was increased from 1 mA in steps of 0.5 mA until: (1) an increase in the amplitude of the last two or three reflexes above a fixed limit of 20 μV for at least 10 ms in the 70–150 ms post-stimulation interval was observed (temporal

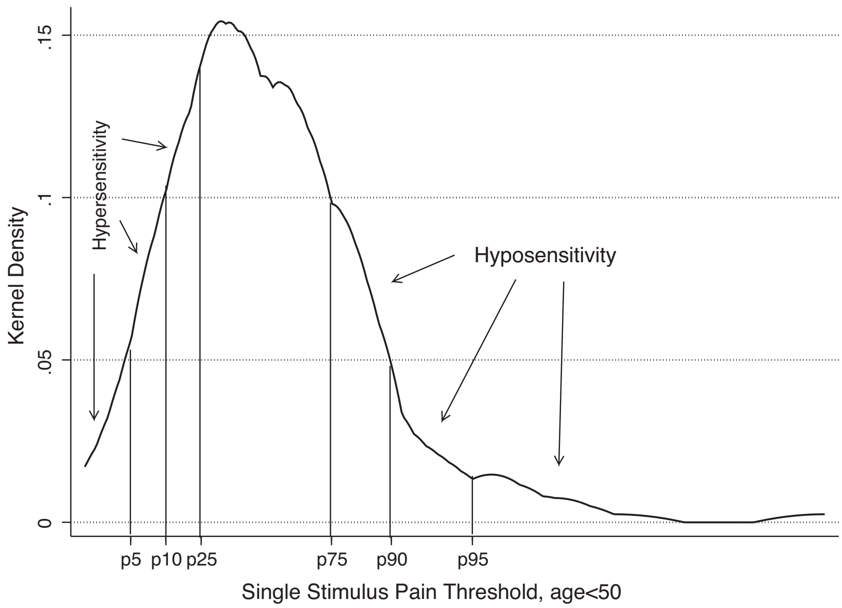

Fig. 1. Illustration of critical values of widespread central hyper- and hyposensitivity. Pain threshold to single electrical stimulation, in patients with age <50 years, is shown. The vertical axis shows the kernel density, which can be interpreted as a continuous and smooth approximation to the histogram of the distribution as the width of the sub-intervals in the histogram becomes very small.

summation reflex threshold); and (2) the subjects felt pain during the last 2–3 of the 5 electrical bursts (temporal summation pain threshold).

2.2.4. Assessment of reflex receptive fields

To evaluate reflex receptive fields (RRF), a previously described procedure was employed [14]. In brief, 10 surface electrodes (15 mm × 15 mm, type 700, Ambu A/S, Denmark) were mounted on the sole of the foot. A computer-controlled electrical relay delivered a stimulus to one of the 10 electrodes in a randomized sequence and double-blind manner. Each stimulus consisted of a constant current pulse train of five individual 1 ms pulses delivered at 200 Hz (Stimulator Noxitest IES 230, University of Aalborg, Denmark). This train of stimuli is felt as single stimulus. The EMG was recorded with surface electrodes (type 720, Ambu A/S, Denmark) over the belly of the tibialis anterior muscle with an inter-electrode distance of 2 cm. First, the pain thresholds were determined for each of the 10 stimulation sites. Then a stimulus intensity equal to 1.5 times higher that the individual pain threshold was delivered. The EMG responses for each stimulation site were recorded from the tibialis anterior muscle. The area of the RRF was calculated using the procedure presented in the previous methodological paper [14]. It is expressed as the area of the foot from which a reflex from a given muscle can be elicited.

2.3. Statistical analysis

The estimates of percentile values of the distribution of the test responses have been obtained by computing quantile regressions for the each pain test. Quantile regression is a statistical method that can be used for the estimation of any percentiles of the response variable [15]. It can be regarded as an extension of multiple regression methods, where instead of estimating the mean of the dependent variables one estimates its quantile distribution. In particular, quantile regression is appropriate for the estimation of the percentile values on either tail of the distribution. These values can be regarded as the critical values of the pain tests, thereby reflecting normative values of the parameters analyzed. Importantly, the quantile regression method that we employed is particularly suited to non-normal distributions of the observations. It is a fully non-parametric method which does not rely on any distributional assumptions, and is therefore robust to non-normality or to any other irregularities in the distribution of the observations.

The role of covariates can be studied by including potential contributing factors as conditioning variables in the quantile regression estimations. In the present analysis, the covariates were gender, age, height, weight, body mass index, body side of testing, depression (Beck Depression Inventory), anxiety (State-Trait-Anxiety-Inventory), catastrophizing (Catastrophizing Scale of the Coping Strategies Questionnaire) and Short-Form 36. The variables according to which critical values have been stratified were chosen on the grounds both of their statistical significance and of their quantitative importance as conditioning factors in the previous study [11].

The quantile regressions have been carried out by using the command *sqreg* in Stata 12. This command generates estimates of quantile regressions with a bootstrapped variance–covariance matrix of the estimates. We computed the 5th, 10th, 25th, 75th, 90th and 95th percentiles of the distributions of the response variables (p^5, p^{10}, p^{25}, p^{75}, p^{90} and p^{95} respectively). For each response variable, all the percentiles have been estimated simultaneously in order to improve statistical efficiency. The number of bootstrapped replications in our calculations has been set equal to 10,000.

3. Results and discussion

3.1. Results

Table 1 reports the estimated percentiles for single stimulus pain threshold, single stimulus reflex threshold, temporal summation pain threshold, temporal summation reflex threshold and RRF area.

The percentiles for single stimulus pain threshold have been stratified by age and the percentiles for single stimulus reflex threshold by body side (dominant *vs.* non-dominant). Gender-stratification was not done, since this parameter was not a significant covariate. This is consistent with previous

Table 1
Descriptive statistics and critical values for parameters of central hypersensitivity and hyposensitivity.

	Mean	Median	SD	Central hypersensitivity			Central hyposensitivity		
				p^{5}	p^{10}	p^{25}	p^{75}	p^{90}	p^{95}
Pain threshold to single electrical stimulation (mA)									
Age ≤ 49	10.3	10	3	6.3	7.3	8.3	12	13.7	16
Age ≥ 50	11.6	12	2.8	9	9	10	13	14	14.7
Reflex threshold to single electrical stimulation (mA)									
Body side: dominant	15.7	16	3.8	10	10.7	13.7	18	19.3	24
Body side: non-dominant	16.6	17	3.6	10.3	12	14.7	18.3	20	22.7
Temporal summation pain threshold (mA)	8.5	8.3	2.2	6	6	7	9.7	11	12
Temporal summation reflex threshold (mA)	8.5	8.3	2.2	6	6	7	9.7	11.3	12
	Mean	Median	SD	Central hypersensitivity			Central hyposensitivity		
				p^{95}	p^{90}	p^{75}	p^{25}	p^{10}	p^{5}
RRF area (proportion of foot sole)	0.44	0.38	0.28	1	0.9	0.62	0.2	0.12	0.08

SD, standard deviation; RRF, reflex receptive field. For RRF, hyper- and hyposensitivity are reflected by high and low values of RRF area, respectively; therefore critical values of RRF area are reverted, compared to the other parameters.

investigations, showing that the influence of gender on pain sensitivity varies according to the type of stimulus applied [16,17].

Fig. 1 illustrates the critical values for one of the tests. In Fig. 2, the critical values for electrical pain threshold are stratified by four age classes for illustration purposes. The statistical analysis conducted on the four age classes was less precise that the analysis on two classes (Table 1); the latter specification (Table 1) may be therefore be preferred to the former one (Fig. 2) for clinical use.

3.2. Discussion

We computed the critical normative values of electrical pain tests for widespread central hypersensitivity and hyposensitivity. The percentiles in Table 1 can be interpreted as the estimates of the statistical distribution of response variables in a pain-free population. For instance, when the single stimulus pain test is applied to individuals with age higher than or equal to 50 years, the pain threshold is estimated to be lower than 6.3 for 5% of the observations (p^5).

The decision of which percentiles to use for the purposes of identifying potentially critical values should consider that the adoption of more extreme values (for instance, those corresponding to p^5 and p^{95}) is more likely to lead to the correct identification of critical observations, but could leave out a number of observations that could also potentially be at risk. In other words, by selecting p^5 and p^{95} one is more likely to obtain a small number of false positives but a potentially large number of false negatives. By contrast, the adoption of critical values that correspond to more central percentiles of the distribution (for instance, p^{25} and p^{75}) would correspond to a smaller number of false negatives, but a potentially larger number of false positives.

The decision on which percentiles to use will therefore depend on the particular clinical picture and the potential consequences of categorizing patients as positive or negative. For instance, if it is believed that the clinical risks of false negatives are greater than the risks of false positives, it would be prudent to adopt less extreme values for the critical percentiles, such as p^{25} and p^{75}. Conversely, if one wants to minimize the risk of false positive, it would be preferable to adopt the extreme percentiles, *i.e.* p^5 and p^{95}.

To date, identifying widespread sensory abnormalities in individual patients has mainly the aim of providing a pathophysiological model that can help patients and clinicians to better understand the mechanisms underlying pain and disability. Furthermore, some data suggest that patients with hyper- or hyposensitivity may be at risk of poor outcome, at least in the field of whiplash injury [2,18]. Identifying these patients may be important to develop therapeutic strategies that prevent poor outcome. Finally, patients with widespread hypersensitivity may theoretically benefit from drugs that attenuate these processes, such as antidepressants, anticonvulsants or NMDA-antagonists; however, we are not aware of controlled studies on such a mechanism-based approach.

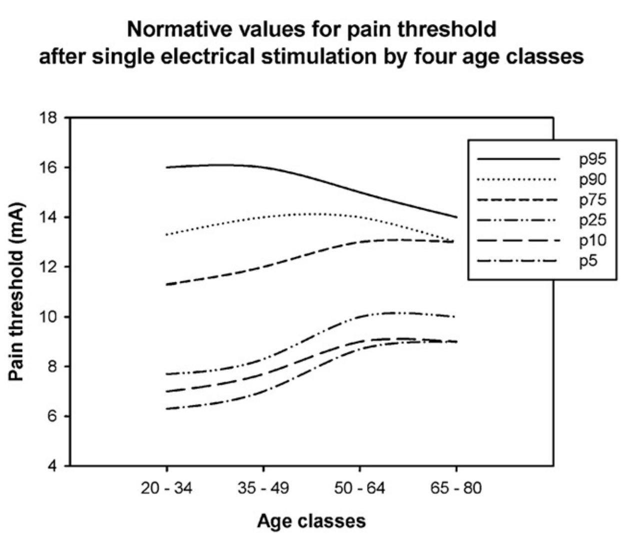

Fig. 2. Illustration of critical values of widespread central hyper- and hyposensitivity stratified by four age classes for pain threshold after single electrical stimulation. Normative values of pain threshold to single electrical stimulation are stratified by four class ages. $p^{5,\ 10\ \mathrm{and}\ 25}$ are the percentile normative values for hypersensitivity, whereas $p^{95,\ 90\ \mathrm{and}\ 75}$ are the percentiles for hypersensitivity.

3.3. Conclusions

Estimates of critical normative values for each electrical pain test in a pain-free population were determined. These values can be used in clinical practice for the assessment of widespread central hyper- and hyposensitivity in individual patients and by future research on mechanism-based treatment of chronic pain conditions.

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Conflict of interest

No author has any conflict of interest related to the content of this paper.

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