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Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity

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Abstract

Pain serves the protection of the body by translating noxious stimulus information into a subjective percept and protective responses. Such protective responses rely on autonomic responses that allocate energy resources to protective functions. However, the precise relationship between objective stimulus intensity, subjective pain intensity, autonomic responses, and brain activity is not fully clear yet. Here, we addressed this question by continuously recording pain ratings, skin conductance, heart rate, and electroencephalography during tonic noxious heat stimulation of the hand in 39 healthy human subjects. The results confirmed that pain intensity dissociates from stimulus intensity during 10 minutes of noxious stimulation. Furthermore, skin conductance measures were significantly related to stimulus intensity but not to pain intensity. Correspondingly, skin conductance measures were significantly related to alpha and beta oscillations in contralateral sensorimotor cortex, which have been shown to encode stimulus intensity rather than pain intensity. No significant relationships were found between heart rate and stimulus intensity or pain intensity. The findings were consistent for stimulation of the left and the right hands. These results suggest that sympathetic autonomic responses to noxious stimuli in part directly result from nociceptive rather than from perceptual processes. Beyond, these observations support concepts of pain and emotions in which sensory, motor, and autonomic components are partially independent processes that together shape emotional and painful experiences.

Keywords: Pain, Brain, Autonomic nervous system, Oscillations, EEG

1. Introduction

Pain is a complex phenomenon that serves the protection of the body. To this end, noxious stimuli translate into a subjective percept and appropriate protective responses. Such protective responses comprise overt motor responses and autonomic responses[33] that allocate energy resources to protective behavior and maintain the integrity and homeostasis of the organism through physiological changes.[27,32,39] Autonomic responses are, thus, an integral component of pain.[23] Previous studies recorded autonomic responses (eg, skin conductance responses and heart rate [HR] changes) to noxious stimuli and showed significant relationships to brain activity in sensorimotor, insular, cingulate and prefrontal cortices, amygdala, hypothalamus, and brain stem.[17,30,34,42,49] Moreover, autonomic responses were related to noxious stimulus intensity[10,15,22,29,51] or subjective pain intensity or both.[10,15,22,29,35,51] However, the precise relationships between objective stimulus intensity, subjective pain intensity, and autonomic responses are not yet clear. In particular, it is unknown whether autonomic responses are more closely related to stimulus intensity or pain intensity. This difference has conceptual implications for the understanding of pain. A closer relationship between stimulus intensity and autonomic responses would imply that autonomic responses result directly from nociceptive rather than from perceptual processes. In contrast, a closer relationship between pain intensity and autonomic responses would suggest that autonomic responses result from perceptual rather than directly from nociceptive processes.

In the present study, we therefore investigated the relationship between noxious stimulus intensity, pain intensity, and autonomic responses by applying tonic noxious heat stimuli to the left and right hands of 39 healthy human participants. The paradigm induces spontaneous dissociations of noxious stimulus intensity and pain intensity[38,48] during which stimulus intensity is encoded by neuronal oscillations at alpha (8-13 Hz) and beta (14-29 Hz) frequencies in the sensorimotor cortex, whereas subjective pain intensity is encoded by gamma oscillations (30-100 Hz) in the prefrontal cortex.[38,48] Thus, the paradigm offers the opportunity to differentially relate stimulus intensity and pain intensity and their cerebral correlates to autonomic responses. The present results show that skin conductance measures during tonic noxious stimulation are more closely related to stimulus intensity than to pain intensity. Correspondingly, skin conductance measures are significantly related to alpha/beta oscillations in contralateral sensorimotor cortex but not to gamma oscillations in medial prefrontal cortex. These findings indicate that sympathetic autonomic responses to tonic pain result directly from nociceptive rather than from perceptual processes.

2. Methods

2.1. Subjects

Fifty-one healthy human subjects (age, 24.7 ± 5.6 years [mean ± SD]; 24 women) participated in the study. All subjects were

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right-handed and gave written informed consent. Due to technical issues with the stimulation device, we excluded data sets of 12 subjects, resulting in a sample size of 39 subjects (age, 24.3 ± 5.6 years; 18 women) for the final analysis. Eight additional right-handed subjects (age, 28.4 ± 5.2 years; 4 women) participated in a control experiment. The study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität München and conducted in conformity with the Declaration of Helsinki. An analysis of the data that focused on the relationships between stimulus intensity, pain intensity, and brain activity has been published previously.[38]

2.2. Paradigm

In 2 *tonic pain* conditions, painful heat stimuli with a duration of 10 minutes were applied to the dorsum of the left (*tonic pain left*) or the right (*tonic pain right*) hand. Apart from the side of stimulation, the 2 tonic pain conditions were identical. Left and right hand stimulations were performed to replicate the findings and to assess whether possible asymmetries reflect left–right or contralateral–ipsilateral asymmetries.

In both conditions, the subjects were instructed to continuously rate the perceived pain intensity on a visual analogue scale ranging from 0 to 100 anchored at *no pain* and *worst tolerable pain* using a custom-built finger-span device with the non-stimulated hand. During the course of stimulation, the scale was presented on a screen by a vertical red bar, the length of which represented the current pain intensity rating.

Painful heat stimuli were applied using a thermode (TSA-II; Medoc, Ramat Yishai, Israel). The time course of stimulation was similar for all subjects, but stimulus intensities were individually adjusted. Stimulus intensity was varied between 3 temperature levels (low, medium, high) of 0.5, 0.8, or 1.1˚C above the individual pain threshold temperature. Thus, the stimulation continuously elicited sensations above pain threshold. The 3 levels were applied using a sequence of 9 plateaus with 3 plateaus at each intensity. At each stimulus intensity, 1 plateau with a duration of 40, 50, and 60 seconds was applied. The order of plateaus was pseudorandomized with the constraints that consecutive plateaus had different stimulus intensities and that the sequence consisted of 3 consecutive triplets of low, medium, and high stimulus intensities. The stimulation started at a baseline temperature of 40˚C; changes of stimulus intensity were implemented with a rate of 0.1˚C/second. The analysis focused on the 8.2-minute interval between the start of the first plateau and the end of the last decrease of stimulus intensity (**Fig. 1**).

The paradigm further comprised 2 *visual control* conditions that were not included in the present analysis and are described in detail elsewhere.[38] The order of the *tonic pain left* and *tonic pain right* conditions was counterbalanced across subjects. The *tonic pain* conditions always preceded the respective *visual control* conditions. Subjects wore headphones playing white noise during all conditions. Stimulus presentation and timing was controlled using Matlab (Mathworks, Natick, MA) and the Psychophysics Toolbox (http://psychtoolbox.org/). For further details of the procedure please refer to Ref. 38.

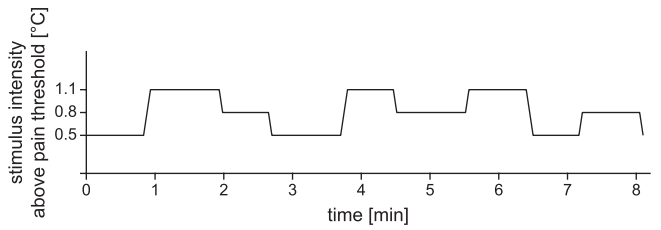

Figure 1. Time course of stimulation included in the analysis. Stimulus intensity varied between 3 temperature levels (low, medium, high) at 0.5, 0.8, or 1.1˚C above the individual pain threshold temperature. At each temperature level, one plateau with a duration of 40, 50, and 60 seconds was applied.

2.3. Autonomic responses

2.3.1. Skin conductance

Skin conductance was recorded at the palmar distal phalanges of the index finger and the middle finger of the stimulated hand. The subjects positioned the stimulated hand comfortably on an armrest and were instructed not to move the stimulated hand during the recording. Ag/AgCl electrodes were filled with isotonic paste and attached by double-sided adhesive rings. The electrodes were attached to a GSR-MR module (Brain Products, Munich, Germany) with constant 0.5 V voltage. Data were recorded in direct current (DC) mode with low-pass filtering at 250 Hz and sampled at 1000 Hz by a BrainAmp ExG MR amplifier (Brain Products). During offline analysis, data were low-pass filtered at 1 Hz using a fourth-order Butterworth filter and downsampled to 512 Hz. The data were visually inspected for artifacts, and periods contaminated with movement artifacts were marked. Two established measures of tonic sympathetic activity[8] were determined: skin conductance level (SCL) and number of spontaneous skin conductance fluctuations (nSF). Skin conductance level was calculated as the mean skin conductance in a 60-second window. In the same window, nSF was determined by counting skin conductance fluctuations with positive deflections greater than 0.05 μS with respect to the preceding trough.[8] Time courses of SCL and nSF were obtained by moving the 60-second window across the data with a step size of 10 seconds. A 60-second window was chosen as an established time interval to obtain tonic skin conductance measures.[8] Consequently, the same window length was used for the analysis of stimulus intensity, pain intensity, HR measures, and brain activity (see below). Windows contaminated with previously marked movement artifacts were discarded.

To rule out local effects due to heat stimulation at the hand ipsilateral to the skin conductance recording, we performed a control experiment that compared skin conductance measures during stimulation of the ipsilateral and contralateral hands. In each subject, skin conductance was recorded either at the left or right hand, while the ipsilateral and contralateral hands were stimulated in 2 separate blocks. The stimulation time courses, which were adapted to the individual pain thresholds, and settings were similar to the main experiment. The subjects were asked to indicate the average pain intensity over the whole stimulation interval on a visual analogue scale ranging from 0 to 100 anchored at *no pain* and *worst tolerable pain* after each block. We counterbalanced the hand for which the threshold was determined, the hand used for skin conductance recording, and the order of left and right hand stimulation across participants. The recording settings and analyses were similar to the main experiment. Skin conductance preprocessing in the main and control experiment was performed using custom Matlab scripts.

2.3.2. Heart rate

The electrocardiogram (ECG) was recorded using a bipolar recording with one electrode placed under the right clavicle and one located below the sternum. Both sites were cleaned with alcohol and abrasive paste before the application of the

Ag/AgCl electrodes. The ECG data were band-pass filtered between 0.016 and 250 Hz and sampled at 1000 Hz by a BrainAmp ExG MR amplifier (Brain Products). Offline, QRS complexes were automatically detected using an established algorithm,[41] except for 1 participant, for whom they were manually marked because of a poor performance of the automated algorithm. A HR time series with a sampling frequency of 512 Hz was computed by extracting the RR interval tachogram and linearly interpolating all time points of an interval between 2 QRS complexes. Similar to the analysis of the SCL, a moving average with a window length of 60 seconds and a step size of 10 seconds was applied to the HR time series. In addition, we investigated HR variability (HRV), which is responsive to noxious stimulation[25] and whose different measures partially selectively reflect sympathetic and parasympathetic activities.[50] We specifically analyzed the square root of the mean squared differences of successive RR intervals (RMSSD) as a time-domain measure and the low- and high-frequency components (LF and HF, respectively) as frequency-domain measures. The HF component has been described to be mostly sensitive to parasympathetic activity, whereas the LF component is mostly sensitive to sympathetic activity or a mixture of sympathetic and parasympathetic activities.[50] Average RMSSD, LF power (0.04-0.15 Hz), and HF power (0.15-0.4 Hz) were obtained for 60-second windows with a step size of 10 seconds using Fast Fourier Transform and a Hanning taper for the frequency-domain measures. Preprocessing of ECG was performed using custom Matlab scripts.

2.4. Electroencephalography

2.4.1. Recordings and preprocessing

EEG data were recorded using an electrode montage of 64 electrodes consisting of all 10–20 system electrodes, and the additional electrodes Fpz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, TP7/8/9/10, P5/6, and PO1/2/9/10, plus 2 electrodes below the outer canthus of each eye (Easycap, Herrsching, Germany) and BrainAmp MR plus amplifiers (Brain Products). All electrodes were referenced to FCz and grounded at AFz. The EEG was sampled at 1000 Hz (0.1 μV resolution) and band-pass filtered between 0.016 and 250 Hz. Impedances were kept below 20 kΩ. Continuous pain ratings and stimulus intensities were fed into the EEG system and recorded with the same sampling frequency.

Preprocessing was performed using BrainVision Analyzer software (Brain Products). EEG data were downsampled to 512 Hz, high-pass filtered at 0.5 Hz, and 50 Hz line noise was removed using a regression approach from the BioSig software library.[53] Eye movements and muscle artifacts were corrected using independent component analysis,[24] and all electrodes were re-referenced to the average reference. Subsequently, time intervals of 400 milliseconds around data points with amplitudes exceeding ±80 μV and signal jumps exceeding ±30 μV were marked for rejection. Additionally, remaining artifacts were identified by visual inspection and marked for rejection.

2.4.2. Time–frequency analysis

EEG data were analyzed using the FieldTrip toolbox[40] and custom programming in Matlab. First, EEG data were band-pass filtered in theta (4-7 Hz), alpha (8-13 Hz), beta (14-29 Hz), and gamma (30-100 Hz) frequency bands using a fourth-order Butterworth filter (forward and backward). Second, time series of frequency-specific brain activity were computed in source space (see next section). Third, the Hilbert transform was applied, and absolute values of the Hilbert transform (ie, the amplitude within the respective frequency band) were computed. In line with the analysis of the autonomic measures, we downsampled and smoothed the amplitude time courses of each frequency band and the time courses of stimulus intensity and pain intensity using a moving average with a window length of 60 seconds and a step size of 10 seconds. EEG data contaminated with artifacts were removed from the windows before the average amplitude was computed (ie, the average amplitude was based on a slightly varying number of data samples depending on the occurrence of EEG artifacts). This procedure was implemented to avoid discarding big parts of the data due to short transient EEG artifacts. Sixty-second windows of EEG data and stimulus or pain intensity with artifacts in skin conductance were discarded.

2.4.3. Source analysis

We used linearly constrained minimum variance beamforming[52] to project the band-pass filtered EEG data from electrode space into source space. Spatial filters were computed based on the covariance matrices of the band-pass filtered data for each frequency band and a lead field matrix. A 3-dimensional grid with a 1 cm resolution covering the brain was defined. The lead field was constructed for each voxel using a realistically shaped 3-shell boundary-element volume conduction model based on the template Montreal Neurological Institute (MNI) brain. We used a regularization parameter of 5% of the covariance matrix and chose the dipole orientation of most variance using singular value decomposition. Finally, the preprocessed EEG data were projected through the spatial filter to extract the time series of neuronal activity of each frequency band at each voxel.

2.5. Relationships between stimulus intensity, pain intensity, autonomic responses, and brain activity

The analyses were performed with the software environment R[46] and the lme4 package.[2] We first investigated the relationships between autonomic responses, stimulus intensity, and pain intensity by calculating linear mixed models (LMMs). The main autonomic response measures (SCL, nSF, HR) were the dependent variables, and stimulus intensity and pain intensity were the independent variables. By including both stimulus intensity and pain intensity as independent variables in each LMM, the relationships to stimulus intensity are always controlled for pain intensity and vice versa. Hence, a significant relationship to stimulus intensity or pain intensity implies that this relationship is significantly stronger for the respective measure than for the other measure. Separate LMMs were calculated for the different autonomic response measures and the *tonic pain left* and *tonic pain right* conditions. All variables were *z*-transformed for each subject using the individual means and SDs of all data samples of the subject. To account for the between-subject variability in the slopes of the relationships, we included random slopes in the LMMs. The slope of the fixed effects was used for statistical testing. The analysis, thus, focused on the relationship between autonomic responses and stimulus or pain intensity within subjects. False discovery rate correction for multiple comparisons across the 3 main autonomic measures was applied.[5] In addition to the main autonomic measures, we statistically tested the relationships of the HRV measures RMSSD, LF, and HF to stimulus intensity and pain intensity.

We performed 2 control analyses. First, to determine the possible influence of autocorrelation on the results, we fitted LMMs with temporally inverted time courses of autonomic responses. Second,

to determine the possible influence of the window length and the resultant smoothing on the results, we calculated LMMs with 50-, 40-, 30-, 20-, and 10-second sliding windows and 10-second step size. False discovery rate correction for multiple comparisons across the 3 main autonomic measures was applied.

In the control experiment, we investigated possible local effects of heat stimulation on skin conductance. To this end, SCL and nSF were compared between stimulation at the hands ipsilateral and contralateral to skin conductance recordings using 2-tailed paired *t* tests.

We next investigated the relationships between autonomic responses and brain activity. We were particularly interested to determine whether skin conductance measures covary with brain activity related to stimulus intensity or pain intensity or both. We therefore used a region of interest (ROI) analysis using voxels and frequency bands in which brain activity has been found to covary with stimulus and pain intensity in our previous study.[38] In particular, we chose ROIs in the bilateral sensorimotor cortex (MNI-coordinates −40, −10, 60; 40, −10, 60) in which we observed significant relationships between alpha and beta oscillations and stimulus intensity. Moreover, we chose a ROI in the medial prefrontal cortex (MNI-coordinates 20, 70, 10) in which we found significant relationships between gamma oscillations and pain intensity. Then, LMMs were calculated with skin conductance measures as dependent variables and the amplitudes of alpha or beta activity in sensorimotor cortex and gamma activity in medial prefrontal cortex as independent variables. Separate LMMs were calculated for the different skin conductance measures and ROIs. Dependent variables and independent variables were *z*-transformed across subjects using the mean and SD of all data samples of all subjects. To account for interindividual differences in the level of skin conductance measures, random intercepts were included in the models. Random slopes were included to account for interindividual differences in the relationships. The slope of the fixed effects was used for statistical testing. The analysis, thus, focused on the within-subject relationships between skin conductance measures and brain activity.

In addition, we performed a whole brain analysis to explore whether other cortical regions showed consistent relationships with skin conductance measures beyond our ROIs. To this end, LMMs were calculated for all voxels and theta, alpha, beta, and gamma frequency bands. Otherwise, the LMMs were identical to the ROI analysis. The final statistical unthresholded *t* maps were rendered to the template MNI brain.

3. Results

Mean pain threshold temperature was 44.7 ± 1.1°C (mean ± SD) in the main experiment, resulting in an average stimulus intensity of 45.5 ± 1.1°C. Average pain ratings of the *tonic pain left* and *tonic pain right* conditions were 53.3 ± 23.0 and 49.6 ± 23.4, respectively. In the control experiment, mean pain threshold temperature was 44.5 ± 1.6°C, resulting in an average stimulus intensity of 45.3 ± 1.6°C. Average global pain ratings over the whole stimulation interval were 60.2 ± 17.3 for left hand stimulation and 59.5 ± 22.6 for right hand stimulation.

We first investigated the relationships between autonomic responses, stimulus intensity, and pain intensity. **Figure 2** shows the group mean time courses of main autonomic responses and stimulus and pain intensity for the *tonic pain left* and *tonic pain right* conditions. To statistically determine the relationships between autonomic responses and stimulus and pain intensity, we calculated LMMs. In particular, by including both stimulus intensity and pain intensity as independent variables, we investigated whether the different autonomic responses (SCL, nSF, HR) were more closely related to stimulus intensity or pain intensity. The results show that the skin conductance measures were significantly related to stimulus intensity when controlling for pain intensity (**Fig. 3**). This finding was consistent for both skin conductance measures (SCL, nSF) and for the stimulation of both hands (*tonic pain left*: SCL, $t = 3.2$, $P = 0.005$, nSF, $t = 3.6$, $P = 0.003$; *tonic pain right*: SCL, $t = 4.0$, $P < 0.001$, nSF, $t = 6.0$, $P < 0.001$). In contrast, neither of the 2 skin conductance measures was significantly related to pain intensity when controlling for stimulus intensity ($P > 0.2$ for *tonic pain left* and *tonic pain right*). Furthermore, HR was neither significantly related to stimulus intensity nor to pain intensity ($P > 0.2$ for *tonic pain left* and *tonic pain right*) and was thus not analyzed further. Thus, for both hands and for both skin conductance measures, skin conductance was more closely related to stimulus intensity than to pain intensity. In addition to the main autonomic measures, we also analyzed the relationship of HRV measures (RMSSD, LF, HF) to stimulus intensity and pain intensity. All HRV measures were neither significantly related to stimulus intensity nor to pain intensity ($P > 0.07$ for all relationships).

Control analyses with inverted time courses of SCL and nSF did not show significant relationships with stimulus intensity (all $P > 0.1$). Thus, the observed relationships between skin conductance measures and stimulus intensity cannot be explained by the autocorrelation of the data. Further control analyses using 50-, 40-, 30-, 20-, and 10-second sliding windows yielded similar results for both SCL (stimulus intensity: all $P < 0.003$; pain intensity, all $P > 0.4$) and nSF (stimulus intensity: all $P < 0.002$; pain intensity, all $P > 0.1$). Thus, the relationships between skin conductance measures and stimulus intensity did not depend on the length of the analysis window. Moreover, in the control experiment, SCL and nSF did not significantly differ between stimulation of the hand ipsilateral and

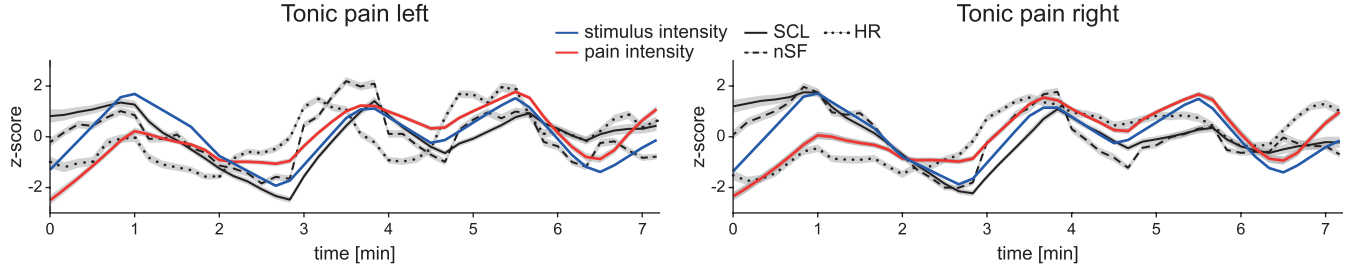

Figure 2. Time courses of autonomic responses, stimulus intensity, and pain intensity averaged across subjects. Data were *z*-transformed within subjects, averaged across subjects, and grand averages were again *z*-transformed. Please note that this transformation was only performed for visualization, whereas for the analysis, data were only *z*-transformed within subjects. Gray shadings indicate the standard error of the mean. SCL, skin conductance level; nSF, number of spontaneous skin conductance fluctuations; HR, heart rate.

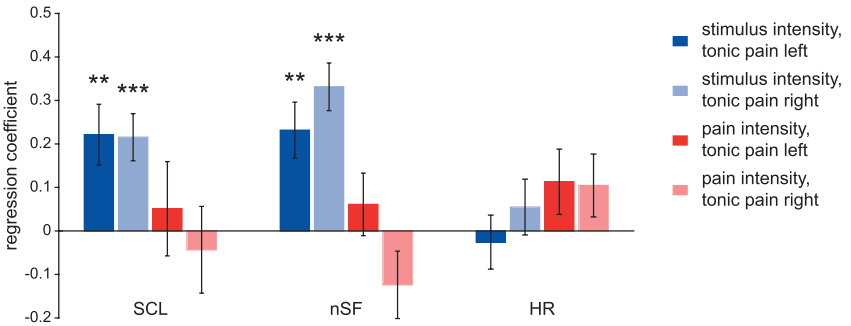

Figure 3. Relationships between autonomic responses, stimulus intensity, and pain intensity. Bars show regression coefficients of the fixed effects from the linear mixed model analyses. Regression coefficients significantly different from zero after correction for multiple comparisons are marked with asterisks. Error bars indicate standard errors of regression coefficients. SCL, skin conductance level; nSF, number of spontaneous skin conductance fluctuations; HR, heart rate. $^{**}P < 0.01$; $^{***}P < 0.001$.

contralateral to skin conductance recordings ($SCL_{ipsilateral}$, 6.3 ± 2.7 μS, $SCL_{contralateral}$, 6.7 ± 3.1 μS, $t_{(7)} = -1.5$, $P = 0.2$, $nSF_{ipsilateral}$, 19.4 ± 18.3, $nSF_{contralateral}$, 23.9 ± 28.9, $t_{(7)} = -0.6$, $P = 0.6$). Hence, it is unlikely that local phenomena due to heat stimulation close to the skin conductance recording site explain the relationships between skin conductance measures and stimulus intensity.

We next investigated the relationship between skin conductance measures and brain activity. We specifically performed ROI-based LMM analyses to assess the relationship between skin conductance measures and neuronal oscillations associated with stimulus intensity and pain intensity (ie, alpha and beta oscillations in sensorimotor cortex and gamma oscillations in medial prefrontal cortex, respectively).[38] The analyses revealed that SCL and nSF negatively covaried with alpha and beta oscillations predominantly in the contralateral sensorimotor cortex (**Fig. 4**; contralateral and SCL: $beta_{tonic\ pain\ left}$, $t = -2.8$, $P = 0.007$; contralateral and nSF: $alpha_{tonic\ pain\ left}$, $t = -2.4$, $P = 0.03$, $beta_{tonic\ pain\ left}$, $t = -2.9$, $P = 0.006$, $beta_{tonic\ pain\ right}$, $t = -2.5$, $P = 0.02$). Furthermore, in the *tonic pain right* condition, SCL negatively related with ipsilateral alpha ($t = -3.7$, $P = 0.001$) and beta oscillations ($t = -2.6$; $P = 0.01$). We observed no association between SCL, nSF, and gamma oscillations in the medial prefrontal cortex ($P > 0.07$). A whole-brain LMM analysis confirmed the relationships between skin conductance measures and alpha and beta oscillations in the sensorimotor cortex predominantly in the hemisphere contralateral to stimulation (**Fig. 5**). No other consistent relationships beyond the ROIs were observed.

4. Discussion

In the present study, we investigated the relationships between objective stimulus intensity, subjective pain intensity, autonomic responses, and brain activity during tonic noxious stimulation in healthy human subjects. The results show that skin conductance

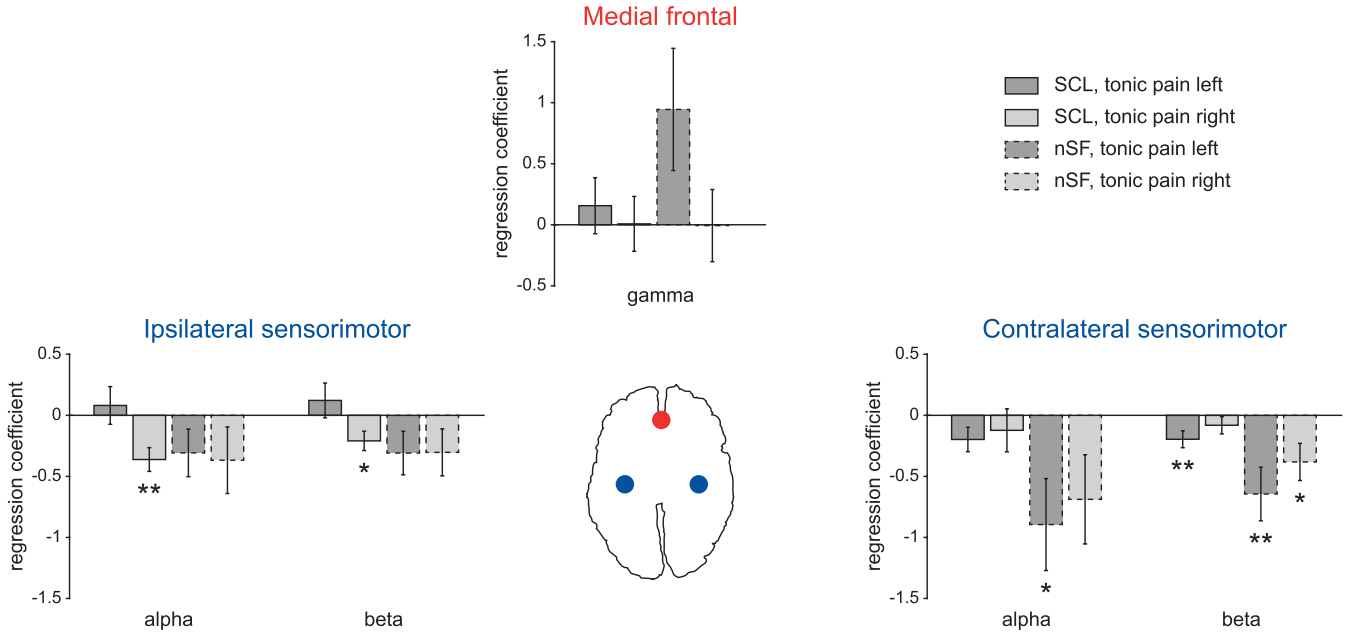

Figure 4. Relationships between skin conductance measures and brain activity (region of interest analysis). The region of interest analysis focused on brain activity associated with stimulus intensity and pain intensity (ie, alpha and beta oscillations in ipsilateral and contralateral sensorimotor cortices and gamma oscillations in medial prefrontal cortex, respectively).[38] Bars show the regression coefficients of the fixed effects from the linear mixed model analyses. Regression coefficients significantly different from zero are marked with asterisks. Error bars indicate the standard error of the regression coefficient. SCL, skin conductance level; nSF, number of spontaneous skin conductance fluctuations. $^{*}P < 0.05$; $^{**}P < 0.01$.

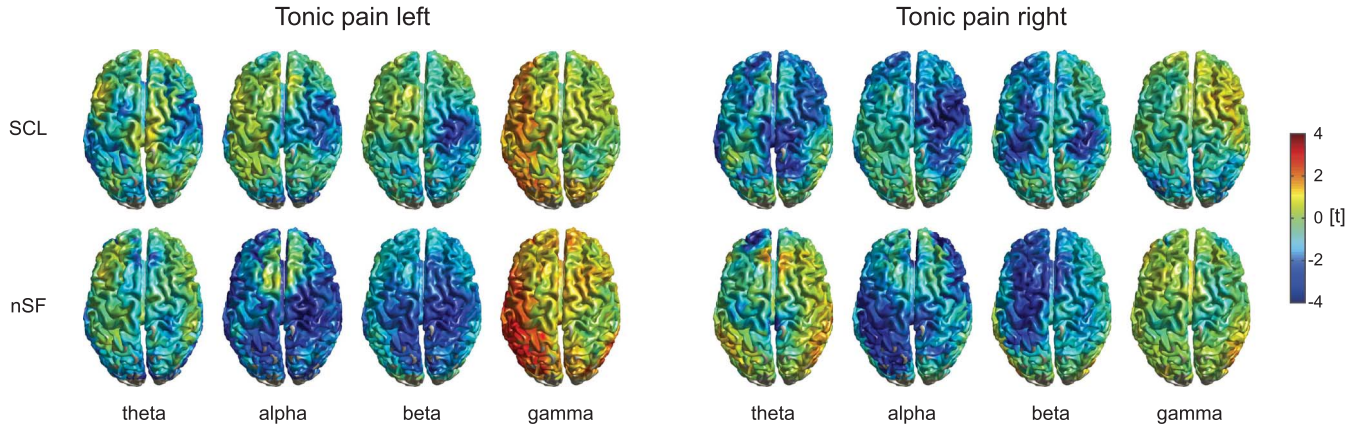

Figure 5. Relationships between skin conductance measures and brain activity (whole-brain analysis). Linear mixed model–based whole-brain *t* maps of the fixed effects showing the relationship between skin conductance measures and neuronal activity at theta, alpha, beta, and gamma frequencies. Maps are not thresholded. SCL, skin conductance level; nSF, number of spontaneous skin conductance fluctuations.

measures are more closely related to stimulus intensity than to pain intensity. Correspondingly, skin conductance measures were more closely related to brain activity associated with stimulus intensity (ie, alpha and beta oscillations in sensorimotor areas) than to brain activity associated with pain intensity (ie, gamma oscillations in medial prefrontal cortex). No significant relationships were found between HR and stimulus intensity or pain intensity. These findings indicate that sympathetic autonomic responses to noxious stimuli do not fully depend on pain perception but that tonic noxious stimuli induce autonomic responses partially independent from perceptual processes.

4.1. Noxious stimulus intensity, pain intensity, and autonomic responses

Previous studies on the relationships between stimulus intensity, pain intensity, and autonomic responses showed significant relationships between stimulus intensity and autonomic responses[10,15,22,29,51] and between pain intensity and autonomic responses.[10,15,22,29,35,51] However, the *differential* relationship between noxious stimulus intensity and autonomic responses on the one hand and between pain intensity and autonomic measures on the other hand has been rarely investigated. Two studies found that skin conductance, pupil diameter,[22] and HR changes[35] were more closely related to pain intensity than to stimulus intensity. However, these studies applied brief heat stimuli with a duration of up to 20 seconds, whereas we applied longer-lasting heat stimuli with a duration of 10 minutes in the present study. Psychophysical[11,45,47] and neurophysiological[48] evidences indicate that the duration of pain critically influences its perceptual characteristics and the underlying neural processes. Thus, the difference in the relationships between autonomic responses, stimulus intensity, and pain intensity between the present and previous studies might be due to different durations of the stimuli. However, the precise mechanisms underlying the effects of stimulus duration on autonomic responses and their relationships to stimulus intensity and pain intensity remain unclear until this relationship has been systematically experimentally addressed. Moreover, the central finding of the present study is not the presence or absence of relationships between autonomic responses and stimulus or pain intensity but rather the significant *difference* in the relationships of autonomic responses to stimulus intensity and autonomic responses to pain intensity.

4.2. Skin conductance and heart rate responses to tonic noxious stimuli

Skin conductance responses are mainly driven by the sympathetic part of the autonomic nervous system,[8,14] which is centrally involved in responses to threat, which are often assessed in stress-related frameworks.[36] In contrast, HR responses are driven by both the sympathetic and parasympathetic branches of the autonomic nervous system.[7] Thus, our observation of a significant relationship between skin conductance responses and stimulus intensity but not between HR and stimulus intensity might indicate a difference between sympathetic and parasympathetic branches of the autonomic nervous system whose functions and cerebral parts differ.[3] Alternatively, the absence of a significant relationship between stimulus intensity, pain intensity, and HR might reflect a lack of sensitivity of the present approach to detect HR changes during tonic pain. Given the many different measures of cardiac psychophysiology[7] and the lack of an established approach to tonic phenomena, this question remains to be answered.

4.3. Autonomic responses to noxious stimuli and brain activity

We found that skin conductance responses to tonic pain were significantly negatively related to neuronal oscillations at alpha and beta frequencies in the contralateral sensorimotor cortex. Current concepts[12] and meta-analyses[3] of cortical autonomic control focus on the role of cingulate and insular cortices rather than sensorimotor areas. However, these concepts mostly refer to autonomic control in general but do not necessarily apply to autonomic responses to tonic noxious stimuli in particular. The latter might involve a sensorimotor component, which is not necessarily included in spontaneous changes of autonomic activity or autonomic responses to stimuli from other modalities. Correspondingly, most[17,34,49] but not all[30,42] studies that specifically addressed the cerebral control of autonomic responses to noxious stimuli also showed significant relationships between the activity of sensorimotor cortices and autonomic responses. Moreover, a recent anatomical study labeled brain pathways controlling sympathetic autonomic activity and showed that a major pathway of autonomic control originated from cortical motor areas.[19] This is well compatible with the present observations. Other brain areas playing a central role in autonomic control, such as the amygdala, the hypothalamus,

and the brain stem,[12] are not adequately captured by EEG due to their deep location and have therefore not been investigated in the present study.

4.4. Limitations

Several limitations apply to the present findings. First, we recorded skin conductance at the same hand where the heat stimuli were applied. This was done as the contralateral hand was used for continuous pain ratings, which would have led to excessive movement artifacts in skin conductance recordings. Therefore, we can not rule out that local phenomena have contributed to the present observations. However, as a control experiment did not show any difference in skin conductance measures between the ipsilateral and contralateral hands, such a contribution is unlikely. Second, our observations apply to the present paradigm using tonic heat pain but do not necessarily generalize to all different types and durations of noxious stimuli. However, the tonic heat pain paradigm yields spontaneous dissociations of stimulus intensity and pain intensity and thereby offers the opportunity to gain insights in the differential relationship of stimulus intensity and pain intensity to autonomic responses. Moreover, tonic pain more closely resembles the main clinical problem of ongoing pain in chronic pain whose perceptual characteristics and cerebral correlates differ from those of phasic experimental pain, which is most common in pain research.[45] Third, we did not find a significant relationship between prefrontal gamma oscillations and autonomic responses. This lack of a significant relationship does not at all preclude that such a relationship exists, which might even reach statistical significance with a higher number of subjects. However, in the present context, the more important finding is that the relationship between alpha and beta oscillations in sensorimotor cortex and autonomic responses is stronger than between prefrontal gamma oscillations and autonomic responses.

4.5. Anatomical substrates and conceptual implications

Anatomically, a close relationship between stimulus intensity and autonomic responses might be served by direct nociceptive pathways to brain areas involved in autonomic control. Important subcortical and brain stem areas of autonomic control include amygdala, hypothalamus, periaqueductal gray, parabrachial nucleus, and the nucleus of the solitary tract.[12] Anatomical studies have shown that all these areas receive direct nociceptive projections,[6,9,16,18,37] which is in good accordance with evidence for a partially parallel organization of pain pathways in the human brain.[1,28,43] The present findings are, thus, well compatible with concepts of pain which propose that sensory, motivational, and autonomic components of pain are partially independent processes that together shape the final evaluation of noxious stimuli.[20,21,31,44] Such concepts of pain parallel recent concepts of emotions, which posit that emotional feelings are shaped by subcortical circuits serving motor and autonomic responses.[13,26] in which sensory, motivational, and autonomic processes partially independently contribute to the final evaluation of pain. These observations might further the conceptual understanding of pain and help to understand abnormal autonomic functions in chronic pain states.[4,54]

5. Conclusions

The present findings show that skin conductance responses to noxious stimuli are more closely related to noxious stimulus intensity and to its cerebral correlates than to pain intensity. The results suggest that autonomic responses to pain do not exclusively result from perceptual but in part directly from nociceptive processes. These findings support concepts of pain

Conflict of interest statement

The authors have no conflict of interest to declare.

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