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*Published in:*  
Somatosensory and Motor Research

*DOI:*  
[10.1080/08990220.2018.1521790](https://doi.org/10.1080/08990220.2018.1521790)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2018

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Bunk, S. F., Lautenbacher, S., Russeler, J., Mueller, K., Schultz, J., & Kunz, M. (2018). Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation? *Somatosensory and Motor Research*, 35(3-4), 192-198.  
<https://doi.org/10.1080/08990220.2018.1521790>

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To cite this article: Stefanie F. Bunk, Stefan Lautenbacher, Jascha Rüsseler, Karin Müller, Jana Schultz & Miriam Kunz (2018) Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation?, Somatosensory & Motor Research, 35:3-4, 192-198, DOI: [10.1080/08990220.2018.1521790](https://doi.org/10.1080/08990220.2018.1521790)

To link to this article: <https://doi.org/10.1080/08990220.2018.1521790>



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## Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation?

Stefanie F. Bunk<sup>a</sup>, Stefan Lautenbacher<sup>b</sup>, Jascha Rüsseler<sup>c</sup>, Karin Müller<sup>b</sup>, Jana Schultz<sup>b</sup> and Miriam Kunz<sup>a</sup>

<sup>a</sup>Department of General Practice and Elderly Care Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; <sup>b</sup>Department of Physiological Psychology, Otto-Friedrich University, Bamberg, Germany; <sup>c</sup>Department of Experimental Psychology, Cognition and Emotion Unit, Otto-Friedrich-University Bamberg, Germany

### ABSTRACT

**Background:** Many researchers have tried to investigate pain by studying brain responses. One method used to investigate pain-related brain responses is continuous electroencephalography (EEG). The objective of the current study is to add on to our understanding of EEG responses during pain, by differentiation between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation.

**Methods:** EEG was recorded during the administration of tonic experimental pain, consisting of six minutes of contact heat applied to the leg via a thermode. Two stimuli above pain threshold, one at pain threshold and two non-painful stimuli were administered. Thirty-six healthy participants provided a subjective pain rating during thermal stimulation. Relative EEG power was calculated for the frequency bands alpha1, alpha2, beta1, beta2, delta, and theta.

**Results:** Whereas EEG activity could not be predicted by stimulus intensity (except in one frequency band), subjective pain sensation could significantly predict differences in EEG activity in several frequency bands. An increase in the subjective pain sensation was associated with a decrease in alpha2, beta1, beta2 as well as in theta activity across the midline electrodes.

**Conclusion:** The subjective experience of pain seems to capture unique variance in EEG activity above and beyond what is captured by noxious stimulus intensity.

### ARTICLE HISTORY

Received 25 July 2018  
Accepted 6 September 2018

### KEYWORDS



Experimental pain; tonic pain; EEG


## Introduction

There is a growing interest in developing objective, non-verbal methods to measure pain in people who are not able to self-report pain; such as people with dementia or people in a minimally conscious state. One way to measure pain non-verbally is by measuring brain activity using electroencephalography (EEG). Continuous EEG has indeed been used to investigate which EEG pattern might be indicative of experimentally induced pain (Huber et al. 2006; Dowman et al. 2008; Nir et al. 2012; Giehl et al. 2014).

Although the findings of the EEG studies are quite promising, results are also contradictory. Reasons for these contradictory findings might be partly due to the various natures of pain being studied (experimental pain vs. clinical pain models). Using experimental pain, studies consistently found a decrease in alpha activity during pain (Huber et al. 2006; Dowman et al. 2008; Nir et al. 2012; Giehl et al. 2014), whereas clinical studies more consistently report an increase in alpha activity in chronic pain patients during rest (for a recent review, see Dos Santos Pinheiro et al. 2016). Another factor contributing to the contradictory EEG findings might

be the definition of pain intensity. When investigating EEG patterns indicative of pain in an experimental setting, there are two ways of operationalizing EEG responses to painful stimulation: (i) by the objective noxious stimulus intensity or (ii) by the subjectively rated pain sensation. Noxious stimulus intensity can for example refer to the degree of Celsius of a heat stimulus. In contrast, subjective pain sensation is measured using rating scales, like Numerical Rating Scales where participants indicate their subjective pain sensation with a number from 0–10. Thus, these two different operationalizations are distinct with regard to that the first may highlight the noxious input side, whereas the second one may stress the psychological output side. In order to investigate whether these different operationalizations of pain intensity (noxious stimulus intensity vs. subjective pain intensity) can explain the contradictory results, studies are needed that include both definitions. So far, two experimental studies compared the effect of noxious stimulus intensity to the effect of subjective pain intensity on EEG signals and found that noxious stimulus intensity and subjective pain intensity might be differentially encoded in EEG activity (Schulz et al.

CONTACT Stefanie F. Bunk  [s.f.bunk@umcg.nl](mailto:s.f.bunk@umcg.nl)  Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, HCP FA21, Postbus 196, 9700 AD Groningen, The Netherlands

 Supplemental data for this article can be accessed [here](#).

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2015; Nickel et al. 2017). The decrease in alpha activity often observed in experimental pain studies was found to be associated with only noxious stimulus intensity, while subjective pain intensity was associated with an increase in gamma oscillations. However, these findings are contrary to another study that showed that alpha activity does correlate with subjective pain intensity (Shao et al. 2012).

The objective of the current study was to add on to our understanding of EEG responses during painful stimulation by differentiation between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation. Five different stimulus intensities were used: two below pain threshold, one at pain threshold and two above pain threshold. In contrast to previous studies, which mostly selected intensities based on physical units (e.g. degree of Celsius), we favoured a more psychological approach by selecting intensities not only based on the individual pain threshold, but also based on just noticeable differences in temperature perception. By using just noticeable differences, we made sure that the five intensities would be perceived differently, while at the same time being as close as possible physically. This strict psychological stimulus definition biases our stimulation more towards the psychological side, whereas previous studies show a bias towards the physical side.

The predictive power of noxious stimulus intensity and subjective pain sensation to explain variance in EEG activity was tested using regression analyses. Since we chose a strict psychological stimulus definition, we aimed to account for this by entering the physical, noxious stimulus intensity first, followed by the subjective pain sensation. We hypothesize that subjective pain sensation can explain variance in EEG power beyond what can be explained by a change in the noxious stimulus intensity.

## Methods

### Participants

Thirty-six participants (18 females, mean age = 22.6 years, SD = 3.2 years) were recruited using bulletins placed throughout the campus of the University of Bamberg. None of the participants was suffering from acute or chronic pain, a psychiatric disease or used analgesics. Participants were asked not to consume alcohol the evening before or on the day of the experiment itself. The study was approved by the ethics committee of the University of Bamberg and a written informed consent was obtained from all participants.

### Experimental procedure

The experimental procedure was composed of several steps. The first step in the current study was to determine the customized stimulation temperatures. In order to determine these, we assessed the individual pain threshold. The individual pain threshold was used in combination with just noticeable difference scores (assessed in a preliminary study) to determine the target temperature of the tonic heat stimuli. Figure 1 shows a schematic overview of the stimulation procedure. Five different heat intensities were used, each lasting for six minutes (Figure

1(A)). Participants received heat stimulation applied to the left thigh while seated in a comfortable chair. EEG was recorded continuously and subjective pain sensation ratings were assessed at the end of each minute (Figure 1(B)). Participants were asked to look at a fixation cross at a computer screen during stimulation to ensure a stable head position and lack of movement that could have affected the EEG signal. Just noticeable differences, the pain threshold, and the tonic heat stimuli are explained in detail below.

### Thermal stimulation

The heat stimuli were administered using a Peltier-based stimulator (Medoc TSA II, Ramat-Yishai, Israel) with a 3 × 3 cm stimulation surface. The thermode was attached to the left thigh with an elastic band. The location of the thermode was changed after each of the five 6-min episodes of stimulation. Therefore, the left dorsal thigh was divided into five equal-sized areas. Given that we decided to use temperature intensities tailored to the individual pain threshold and that we also took into account just noticeable differences (JNDs) in pain perception, pain threshold and JND had to be assessed beforehand.

*Just noticeable differences.* JNDs refer to the magnitude of the smallest difference between two stimuli of differing intensities that the participant is able to detect. We decided to assess JNDs in a preliminary study with 20 different participants. The reasons for this were that the JND assessment was time consuming and the results of the preliminary study showed good stability (coefficient of variation, CV = 0.285) so that we could use the values in the present study. To determine JNDs, we used the method of limits. The temperature of the thermal probe increased from a starting temperature of 32 °C at a rate of 0.3 °C/s and participants were instructed to press a stop button as soon as they noticed a difference in temperature. This difference is the JND. Pressing the stop button resulted in the temperature returning back to baseline. JNDs were assessed across a range of starting temperatures (32 °C–45 °C, with 1 °C difference between each starting temperature). The average JND values are shown in

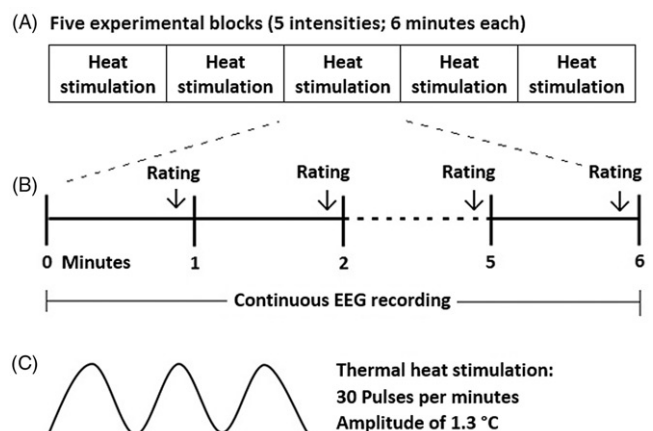
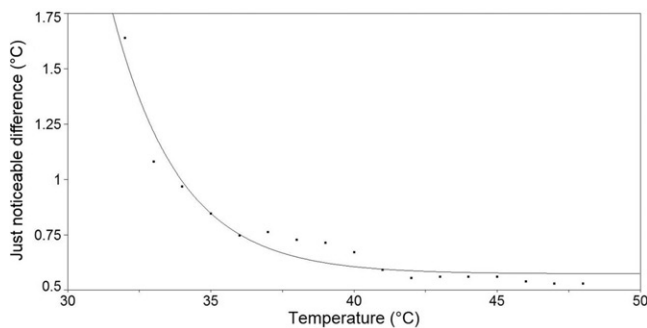


Figure 1. Schematic overview of the experimental procedure. (A) The procedure consisted of five experimental blocks, in which participants received painful stimulation lasting for six minutes. During each block, a different heat intensity was used. (B) Pain was rated during the last five seconds of each minute of stimulation. EEG was recorded continuously. (C) The heat stimuli were oscillating with 30 pulses per minute and an amplitude of 1.3 °C, with the target temperature being reached at the peak.



**Figure 2.** Just noticeable difference (JND) curve. JND describes the objective change in temperature that is needed for a person to notice this change subjectively. It depends on the starting temperature, with higher starting temperatures leading to smaller JNDs. The JND values are derived from a pilot study, where we assessed JND in a group of 20 participants. The results were extrapolated to obtain a JND curve.

**Figure 2.** These values were then extrapolated to obtain a JND curve over the various starting temperatures. This curve is also shown in **Figure 2**.

**Pain threshold.** Individual pain thresholds were assessed directly above the knee using the method of adjustment in six trials. The method of adjustment is frequently used in studies applying tonic pain stimulation (Kleinböhl et al. 1999; Giehl et al. 2014; Horn-Hofmann et al. 2015). Participants were asked to adjust a temperature starting from 36°C, using heating and cooling buttons, until they obtained a level which was barely painful. A constant press of the buttons resulted in the heating or cooling of the probe at a rate of 0.7°C/s. The first two trials served as an exercise. The average of the last four trials was considered as the pain threshold.

**Tonic heat stimulation.** JNDs and the individual pain threshold values were used to define the target temperatures of the tonic heat stimuli for each participant. The estimated JND curve was used to determine the participant's JND, based on the participant's pain threshold. The five stimulus intensities that we used were: pain threshold minus 2\*JND (-2JND), pain threshold minus 1\*JND (-1JND), pain threshold, pain threshold plus 1\*JND (+1JND) and pain threshold plus 2\*JND (+2JND). Using JNDs, we are assured that we use the smallest differences between intensities that participants are still able to detect. The stimuli were presented in a pseudo-randomized order.

For tonic heat stimulation we used the tonic heat pain model, which makes it possible to produce tonic pain perception over lengthy periods (6 min) without reaching pain tolerance level. This model has been described in detail before (Lautenbacher et al. 1995). In short, the temperature started at a baseline of 36°C and increased with a rate of 0.5°C/s until the target temperature was reached. The stimuli of the tonic heat pain model consisted of small heat pulses with a constant frequency of 30 pulses/min (**Figure 1(C)**). The temperature was then oscillating with an amplitude of 1.3°C (target temperature being reached at the peak) for six minutes.

### Pain ratings

Pain sensation was rated during the last five seconds of each minute of stimulation (**Figure 1(B)**). This resulted in six ratings

per tonic stimulus, which were averaged to obtain one subjective pain sensation for each stimulus intensity. A numerical rating scale (NRS) was used, which was displayed on a computer screen. This scale ranged from 0 to 10, in which 0 was defined as 'no sensation', 5 as 'slightly painful' and 10 as 'extremely intense pain'. Accordingly, all painful stimuli should be rated with 5 or higher number, and all non-painful stimuli should be rated by a number lower than 5.

### EEG recording and analysis

EEG was recorded during the administration of the thermal stimuli. Eleven electrodes were affixed according to the 10/20 convention using the ECI Electro-Cap Electrode system (Electro-Cap International, USA), which was available in three sizes. Before attaching the electrodes, the scalp was prepared with alcohol to reduce resistance and participants were instructed to move as little as possible during recording. Our aim was to use an analysis approach that is more easy to apply and thus, has the potential to also be used in more clinical settings (e.g. to assess pain in non-verbal patients with dementia). To this aim, only three electrodes were used for further analyses. So far, there seems to be no specific electrodes that show a consistent association with pain across all studies. Since we wanted to cover at least anterior, middle and posterior regions of the brain, we decided to use the electrodes placed on the midline (Fz, Cz and Pz). We decided on midline electrodes because lateral electrodes would have increased the number of electrodes (given right and left sites). The Cz electrode served as a reference during EEG recording, but this was then re-referenced to two electrodes attached to the mastoid bones. Two referential electrodes were connected to the mastoids and a ground electrode to the forehead above the nasion. The electrooculography (EOG) was recorded for detection of eye movement artefacts with electrodes in the horizontal axis. Impedance was controlled to be lower than 5 kΩ. The EEG signals were recorded, amplified and analysed respectively using BrainVision Recorder, BrainVision V-Amp and BrainVision Analyzer (Brain Products) software. Per minute of stimulation, three 2-second long artefact-free epochs were taken for analysis. This resulted in 18 epochs per stimulus intensity (6 min × 3 epochs). The criteria for the selection were no eye movements registered by the EOG and no apparent disturbances or irregularities in the EEG signal on visual inspection. Furthermore, no epoch was taken from the last 5 s of a recording minute, as the pain ratings were given during this time. Spectral analysis was performed using Fast Fourier Transform. Relative power spectra were calculated for each electrode for the frequency bands delta (0.5–3.5 Hz), theta (4–7 Hz), alpha1 (7.5–9.5 Hz), alpha2 (10–12 Hz), beta1 (13–23 Hz), and beta2 (24–34 Hz). The relative power of all 18 epochs per stimulus intensity were averaged to obtain a single power value for each stimulus intensity, separately for each frequency band and electrode.



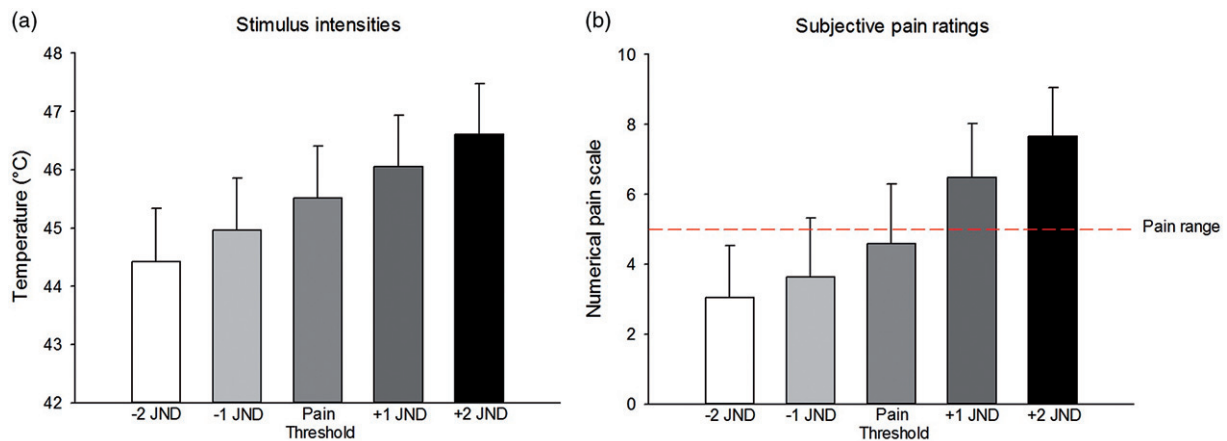


Figure 3. Mean values ( $\pm$ SD) of (A) stimulus intensities applied during tonic stimulation and (B) of the subjective pain ratings. JND: Just noticeable difference.

### Statistical analysis

**Subjective pain sensation.** Analyses of variance with repeated measures were conducted to examine whether the five stimulus intensities were rated significantly different as well as to confirm that the selected intensities elicited sensations in the expected range (non-painful as well as painful sensations).

**Association between EEG power and stimulus intensity/subjective pain sensation.** Multiple block wise linear regression analyses were conducted to examine whether stimulus intensity and/or subjective pain sensation could explain variance in EEG power. Regression analyses were performed for each frequency band separately using EEG power as the dependent variable. To control for electrode site (Fz, Cz, Pz), electrode site was entered as a dummy variable in the first step. In the second step (step 2), stimulus intensity was entered. In the last step (step 3), subjective pain sensation (ratings) was entered in the regression analyses to investigate whether subjective pain sensation can explain variance in EEG power beyond what can be explained by stimulus intensity. Statistical analyses were performed using IBM SPSS Statistics 24 (Armonk, NY). Alpha level was set to 0.05.

## Results

### Stimulus intensities

The mean pain threshold was  $45.51^{\circ}\text{C}$  ( $\text{SD}=0.90$ ). The five stimulus intensities, which were based on the individual pain threshold and JND, ranged from an average of  $44.42^{\circ}\text{C}$  ( $-2\text{JND}$ ;  $\text{SD}=0.92$ ) to an average of  $46.60^{\circ}\text{C}$  ( $+2\text{JND}$ ;  $\text{SD}=0.88$ ) (see Figure 3(A)).

### Subjective pain sensation

As can be seen in Figure 3(B), subjective pain ratings (NRS scale) increased significantly across the five stimulus intensities ( $F(4,140)=108.5$ ,  $p<.001$ ). As intended, the two temperatures below pain threshold were on average rated as non-painful, whereas the two temperatures above pain threshold were on average rated as painful.

### Stimulus intensities and subjective pain sensation predicting EEG responses

Multiple block wise linear regression analyses were conducted to examine whether stimulus intensity and/or subjective pain sensation could explain variance in EEG power during tonic heat stimulation for the frequency bands alpha1, alpha2, beta1, beta2, theta, and delta. The results of each frequency band are reported below and in Table 1. The average EEG power values can be found in the Supplemental material.

**Alpha1.** After controlling for electrode site, stimulus intensity did not lead to a significant increase in explained variance of alpha1 power (Table 1). When entering subjective pain sensation to the model in the third step, we also did not find a significant increase in explained variance. Thus, we found no evidence that stimulus intensity or subjective pain sensation are related to alpha1 power during tonic heat stimulation.

**Alpha2.** After controlling for electrode site, stimulus intensity again did not lead to a significant increase in explained variance of alpha2 power (Table 1). However, when entering subjective pain sensation to the model in the third step, we did find a significant increase in explained variance of 2%, with increased pain sensation being related to a decrease in alpha2 power. Thus, our results indicate that subjective pain sensation is significantly related to alpha2 power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to alpha2 power.

**Beta1.** After controlling for electrode site, stimulus intensity again did not lead to a significant increase in explained variance of beta1 power (Table 1). As we found for alpha2 power, entering subjective pain sensation to the model in the third step led to a significant increase in explained variance (5%), with increased pain sensation being related to a decrease in beta1 power. Thus, our results indicate that subjective pain sensation is significantly related to beta1 power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to beta1 power.

**Beta2.** Again, only subjective pain sensation led to a significant increase in explained variance of 2% (see Table 1), with increased pain sensation being related to a decrease in beta2 power. Thus, our results indicate that subjective pain sensation is significantly related to beta2 power during tonic

**Table 1.** Results of the multiple linear regression analyses.

	Step	Predictor variable	$\beta$	$t$	Statistics – overall			Statistics – change in the model	
					$R^2$	$F$	$p$	$\Delta R^2$	$p$
$\alpha 1$	1	Electrode site*			0.11	31.65	<.001	0.11	<.001
	2	Stimulus intensity	–0.01	–0.16	0.11	21.06	<.001	<0.01	.940
	3	Pain sensation	0.01	0.15	0.11	15.77	<.001	<0.01	.885
$\alpha 2$	1	Electrode site*			0.05	16.06	<.001	0.06	<.001
	2	Stimulus intensity	0.17	2.73	0.05	10.69	<.001	<0.01	.937
	3	Pain sensation	–0.22	–3.64	0.07	11.52	<.001	0.02	<b>&lt;.001</b>
$\beta 1$	1	Electrode site*			0.02	4.20	.015	0.02	.015
	2	Stimulus intensity	0.25	4.07	0.02	2.83	.038	<0.01	.739
	3	Pain sensation	–0.32	–5.22	0.06	9.05	<.001	0.05	<b>&lt;.001</b>
$\beta 2$	1	Electrode site*			0.01	1.61	.201	0.01	.201
	2	Stimulus intensity	0.18	2.91	0.01	1.55	.200	<0.01	.231
	3	Pain sensation	–0.18	–2.85	0.02	3.21	.013	0.02	<b>.005</b>
$\delta$	1	Electrode site*			0.02	5.84	.003	0.02	.003
	2	Stimulus intensity	–0.14	–2.15	0.03	5.38	.001	0.01	<b>.037</b>
	3	Pain sensation	0.06	0.99	0.03	4.28	.002	<0.01	.319
$\theta$	1	Electrode site*			0.02	4.87	.008	0.02	.008
	2	Stimulus intensity	0.14	2.20	0.02	3.24	.022	<0.01	.924
	3	Pain sensation	–0.19	–3.09	0.04	4.85	.001	0.02	<b>.002</b>

\* $\beta$  and  $t$  values cannot be reported for 'electrode site' because the three electrode sites were entered as dummy variables.

Analyses were performed for each frequency band ( $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$ ,  $\beta 2$ ,  $\delta$  and  $\theta$ ) using EEG power as the criterion variable. In step 1, electrode site was entered as dummy variables. In step 2, stimulus intensity was entered as a predictor variable. In step 3, subjective pain sensation was entered as a predictor variable. Significant  $p$  values are presented in bold.

heat stimulation, but we found no evidence that stimulus intensity is related to beta2 power.

*Theta.* Yet again, only subjective pain sensation significantly added explained variance of 2% to the model (Table 1), with increased pain sensation being related to a decrease in theta power. Thus, our results indicate that subjective pain sensation is significantly related to theta power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to theta power.

*Delta.* In contrast to the other frequency bands, stimulus intensity did lead to a significant increase in explained variance of 1% in the delta band, with increased stimulus intensity being related to a decrease in delta power (Table 1). However, subjective pain sensation did not show a significant association with delta power. Thus, our results indicate that stimulus intensity is significantly related to delta power during tonic heat stimulation, but we found no evidence that subjective pain sensation is related to delta power.

*Summary.* Overall, stimulus intensity could only explain variance in EEG power in one frequency band, namely, the delta frequency band. In contrast, subjective pain sensation could significantly predict the power of several frequency bands during tonic heat stimulation. Subjective pain sensation could predict EEG power for the frequency bands alpha2, beta1, beta2, and theta. The relation between subjective pain sensation and EEG power during tonic heat stimulation was negative for every of these frequency bands. This means that an increase in subjective pain sensation was associated with a decrease in EEG activity in these frequency bands.

## Discussion

The aim of this study was to add on to our understanding of EEG responses to painful stimulation by differentiation

between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation. The unique part of our study is the approach that was used to select the stimulus intensities. Whereas previous studies mostly selected intensities based on physical units (e.g. degree of Celsius), thus showing a bias towards the physical characteristics of the stimuli (the input side of nociceptive processing); we selected intensities purely based on perception, thus biasing our approach towards the psychological side (the result of nociceptive processing). More precisely, individual pain thresholds and JND units were used to obtain stimulus intensities that increased with subjective equal steps. This sets us apart from previous studies.

### EEG patterns indicative of the subjective pain sensation

In line with our expectations, subjective pain sensation could explain parts of the variance in EEG power in several frequency bands, namely alpha2, beta1, beta2, and theta. In all of the frequency bands, EEG power was lower when the stimulus was rated more painful. In general, this is in agreement with studies which selected their pain intensities based on physical units (Nir et al. 2012; Shao et al. 2012; Peng et al. 2014). One experimental study used cold water to induce pain (Shao et al. 2012) and found that subjective pain sensation was negatively correlated with EEG power in the same frequency bands as in our study. Moreover, negative correlations between alpha power and subjective pain sensation were also found in studies using experimental heat pain (Nir et al. 2012; Peng et al. 2014). Thus, regardless of whether one uses a stimulation approach that is more focussed on the psychological side (our approach) or on the physical side (e.g. Shao et al. 2012), an increase in subjective pain sensation has been found to be associated with a decrease in EEG

power. However, contradictory findings have also been reported. Two other studies found that pain sensation was associated with an increase (and not a decrease) in the EEG response, namely, in the gamma frequency band (Schulz et al. 2015; Nickel et al. 2017).

### ***EEG patterns indicative of the noxious stimulus intensity***

When looking at the association between EEG power and stimulus intensity, we observed that stimulus intensity could partly explain variance in EEG power in the delta frequency band. This is in accordance with previous findings (Ferracuti et al. 1994; Chang et al. 2002; Huber et al. 2006; Giehl et al. 2014). In other frequency bands, however, we did not find a significant association between stimulus intensity and changes in EEG power. This is in contrast to the majority of previous studies, which found significant associations between stimulus intensity and EEG power for several frequency bands. Besides delta, alpha power has continuously been found to be negatively associated with stimulus intensities (Chen and Rappelsberger 1994; Ferracuti et al. 1994; Chang et al. 2002; Huber et al. 2006; Dowman et al. 2008; Nir et al. 2012; Shao et al. 2012; Giehl et al. 2014). How can this contradiction between our and previous studies be explained? One possible explanation is that selecting stimulus intensities based on JNDs resulted in very small differences between stimulus intensities (approximately 0.5°C). Previous studies often used much larger differences between stimulus intensities, ranging between 1.3°C and 13.4°C for heat stimuli (Huber et al. 2006; Nir et al. 2012; Giehl et al. 2014) up to 30°C for cold pain (Dowman et al. 2008; Shao et al. 2012). Thus, using very small differences between stimulus intensities as we did in the present study, we could not confirm previous findings of strong associations between stimulus intensities and EEG power. On the other hand, the findings of previous studies are also not consistent. With regard to the delta frequency for example, some studies did find changes in EEG power during painful stimulation, while other studies could not demonstrate this (Dowman et al. 2008; Shao et al. 2012). The stimulation protocol, stimulus intensity and electrode locations often differ between studies, and are likely a major factor leading to the different results between studies. This has made it challenging to find a common EEG pattern of pain.

### ***Noxious stimulus intensity versus subjective pain sensation***

Using block wise regression analyses, we could show that subjective pain sensation can explain variance in EEG power beyond what can be explained by stimulus intensity. In accordance with the present finding, previous studies have demonstrated that subjective pain sensation is differentially encoded in EEG activity compared to stimulus intensity (Schulz et al. 2015; Nickel et al. 2017). Whereas, subjective pain sensation was associated with an increase in gamma oscillations in the medial prefrontal cortex, stimulus intensity

was found to be associated with a decrease in alpha and beta oscillations in the sensorimotor cortex. In contrast to these two studies, gamma oscillations were not included in our study. Assessing gamma frequency is challenging because neuronal signals in this frequency band are highly contaminated by non-cerebral electrical sources (noise), which means that the signal-to-noise ratio is quite small (Luck 2004), thus making it difficult to capture a good signal. With our study we decided to focus on the more robust frequency bands (alpha, beta, delta, theta) that are less sensitive to noise. Furthermore, the type of analysis (simple power analysis vs. time-frequency/source analysis) was different in our study. It is therefore difficult to directly compare our findings to these studies. Nevertheless, there seems to be enough evidence to support the notion that subjective pain sensation and physical stimulus intensity both capture unique variance in EEG activity.

It is difficult to directly translate the findings of the current study to relevant suggestions for future clinical practice. One implication surely is that when searching for EEG patterns that are indicative of pain, one should always assess the subjective report of the person in pain regardless of whether one uses experimental pain induction or clinical pain models; given that subjective pain sensation captures unique variance in EEG activity that is independent of the noxious input. With regard to an endeavour to use EEG signal in clinical practice to measure pain more objectively, our findings suggest that a simple recording with only a few electrodes and only looking at changes in EEG power might not be enough to capture pain specific changes in EEG activity. For example, we and others have found that a decrease in alpha activity is associated with an increase in pain perception (Nir et al. 2012; Shao et al. 2012; Peng et al. 2014). However, changes in alpha power are not only specific to pain but can be found in various affective and cognitive states (e.g. alpha power is related to memory performance (Klimesch 1999)). Thus, more elaborated recordings (e.g. more recording sites) as well as more elaborated analyses (e.g. analysis of neuronal oscillations and synchrony) are necessary in order to come closer to a pain-specific EEG pattern that could be used to assess pain in clinical practice. However, such elaborated measures might hinder clinical usefulness because they are not easy to use.

### ***Limitations***

One important limitation is that we limited our analyses to three EEG electrodes, whereas other studies used a higher number of recording electrodes covering a broader surface of the brain. We wanted to reduce type II error (analyzing the EEG data for various recording sites would have substantially increased the number of analyses) and we aimed for an easy to use analysis approach (making it more useful for clinical practice). However, the disadvantage is that this small number might have limited the likelihood of finding effects. Indeed, the effects we found were rather small, with the highest explained variance being only 5%. The second limitation is that we used an averaged pain sensation over time



for the statistical analyses instead of using the subjective pain sensation for each minute, which might have resulted in more precise findings. However, we decided to not analyse the data per minute because this would have increased the number of analyses by factor six. Moreover, the pain sensation across the six minutes was also quite stable. Although there were significant changes over time, these were rather small, with an average decrease of 0.9 on the NRS at the lowest tonic heat intensity and an average increase of 0.5 on the NRS for all remaining heat intensities.

## Conclusion

In conclusion, we observed that EEG power during painful stimulation occurring across the midline of the brain mirrors more closely the subjective pain sensation than the stimulus intensity. Subjective pain sensation could explain variance in several frequency bands beyond what could be explained by stimulus intensity. This is likely due to the way we selected stimulus intensities, biasing our stimulation towards the psychological, compared to the physical side. Using this stimulation approach, we find that EEG activity mirrors more closely the psychological output side (ratings), than the physical input side (stimulus intensity) of nociceptive processing.

## Disclosure statement

No potential conflict of interest was declared by the authors.

## Funding

This study was supported by a FNK grant of the University of Bamberg.

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