Cerebral Cortex May 2012;22:1118–1123
doi:10.1093/cercor/bhr186
Advance Access publication July 17, 2011

Decoding an Individual's Sensitivity to Pain from the Multivariate Analysis of EEG Data

Enrico Schulz[1], Andrew Zherdin[2], Laura Tiemann[1], Claudia Plant[2,3] and Markus Ploner[1]

[1]Department of Neurology and [2]Department of Neuroradiology, Technische Universität München, 81675 Munich, Germany and [3]Department of Scientific Computing, Florida State University, Tallahassee, FL 32306-4120, USA

Address correspondence to Dr Enrico Schulz, Department of Neurology, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany. Email: eschulz@lrz.tum.de.

The perception of pain is characterized by its tremendous intra- and interindividual variability. Different individuals perceive the very same painful event largely differently. Here, we aimed to predict the individual pain sensitivity from brain activity. We repeatedly applied identical painful stimuli to healthy human subjects and recorded brain activity by using electroencephalography (EEG). We applied a multivariate pattern analysis to the time–frequency transformed single-trial EEG responses. Our results show that a classifier trained on a group of healthy individuals can predict another individual's pain sensitivity with an accuracy of 83%. Classification accuracy depended on pain-evoked responses at about 8 Hz and pain-induced gamma oscillations at about 80 Hz. These results reveal that the temporal–spectral pattern of pain-related neuronal responses provides valuable information about the perception of pain. Beyond, our approach may help to establish an objective neuronal marker of pain sensitivity which can potentially be recorded from a single EEG electrode.

Keywords: electroencephalography, gamma oscillations, interindividual variability, multivariate pattern analysis, pain sensitivity

Introduction

Pain is a complex sensory experience which does not simply reflect sensory information but can be substantially influenced by the individual sensitivity to pain. Some individuals perceive a sensory event as strongly painful whereas others perceive the very same event as only marginally painful (Lanier 1943; Coghill et al. 2003; Nielsen et al. 2009). Such differences in the sensitivity to pain influence future pain experiences, the development of chronic pain syndromes, and responses to analgesic treatment (Edwards 2005; Nielsen et al. 2009). An objective neuronal marker of pain sensitivity could, thus, help to prevent, diagnose, and treat painful conditions (Borsook et al. 2010; Tracey 2011).

In the brain, the complex perception of pain is subserved by an extended network of brain areas (Apkarian et al. 2005; Tracey and Mantyh 2007). Recent neurophysiological studies disclosed different partially overlapping pain-related neuronal responses within this network. These pain-related neuronal responses include evoked responses at theta frequencies (3–8 Hz) (Garcia-Larrea et al. 2003; Lorenz and Garcia-Larrea 2003) and induced responses at gamma (~80 Hz) (Gross et al. 2007; Hauck et al. 2007) and alpha (~10 Hz) (Mouraux et al. 2003; Ploner et al. 2006) frequencies. A few studies related differences in pain sensitivity to brain activity. A functional magnetic resonance imaging (fMRI) study indicated that pain-related blood oxygen level–dependent (BOLD) responses in somatosensory, anterior cingulate, and prefrontal regions reflect the subject's sensitivity to pain (Coghill et al. 2003). Neurophysiological studies showed that the individual pain sensitivity correlates with amplitudes of evoked responses at theta frequencies (Iannetti et al. 2005; Schulz et al. 2011). It should, thus, in principle be possible to infer an individual's sensitivity to pain from pain-related brain responses.

Considering the multitude of pain-related neuronal responses, multivariate approaches which analyze complex patterns of information appear particularly promising for decoding the sensitivity to pain from brain activity. Such multivariate "brain reading" approaches have recently been used to identify patterns of brain activity that differentiate between mental states (Haynes and Rees 2006; Norman et al. 2006; Lotte et al. 2007). Researchers have successfully inferred visual percepts, speech content, or even hidden intentions from fMRI data (e.g., Haxby et al. 2001; Haynes and Rees 2005; Formisano et al. 2008; Kay et al. 2008). A recent study applied multivariate pattern analysis (MVPA) to pain and showed that it is possible to distinguish different levels of painful and nonpainful stimulation based on fMRI data (Marquand et al. 2010). However, that study pursued an intraindividual approach, that is, a classifier was trained on and applied to data from the same subject. In contrast, most practical applications require cross-subject approaches, that is, a classifier is trained on a group of subjects and then used to predict another individual's mental state. Moreover, it would be particularly desirable to not only distinguish different stimuli but to infer how different individuals perceive objectively identical stimuli from brain activity.

Here, we therefore applied identical painful stimuli to a group of healthy human subjects. In a cross-subject brain reading approach, we aimed to decode an individual's pain sensitivity from the temporal–spectral pattern of neuronal responses as assessed by time–frequency transformed electroencephalographic (EEG) data. To this end, an MVPA technique was trained on the single-trial EEG data of healthy human subjects to investigate whether it is possible to predict another individual's pain sensitivity from brain activity.

Materials and Methods

Subjects

Twenty-three healthy human subjects (9 males, 14 females) with a mean age of 26 years (range 19–35 years) participated in the study. Informed consent was given by all subjects. The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

Paradigm

Sixty painful cutaneous laser stimuli of identical intensity were delivered to the dorsum of the right hand. The laser device was a Nd:YAP laser (Electronical Engineering, Florence, Italy) with a wavelength of 1340 nm, a pulse duration of 3 ms, and a spot diameter of 6 mm. Stimulus intensity was kept constant at 2750 mJ, which evoked slightly to moderately painful pinprick-like sensations.

Stimulation site was slightly changed after each stimulus. Interstimulus intervals (ISIs) were randomly varied between 8 and 12 s. The subjects passively perceived the stimuli with closed eyes. Three seconds after stimulus application, the subjects were prompted by an auditory cue to verbally rate the pain intensity on a numerical rating scale between 0 (no pain) and 10 (maximum tolerable pain). Pain ratings were used to assign "true" labels of pain sensitivity to each individual. To this end, trials were split around the mean of the 11-point numerical rating scale. Subjects who rated >5 ("high pain") more often than ⩽5 ("low pain") were labeled "pain sensitive" and subjects who rated ⩽5 more often than >5 were labeled "pain insensitive."

EEG Recordings and Analysis

EEG data were recorded using an electrode cap (EASYCAP, Herrsching, Germany). The electrode montage included 64 electrodes consisting of all 10–20 system electrodes and the additional electrodes Fpz, FCz, 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, TP7/8/9/10, P5/6, PO1/2/9/10, plus 2 electrodes below the outer canthus of each eye. The EEG was referenced to the FCz electrode, grounded at AFz, sampled at 1 kHz (0.1 μV resolution), and high-pass filtered at 0.1 Hz. The impedance was kept below 20 kΩ.

The raw EEG data were preprocessed in BrainVision Analyzer software (Brain Products, Munich, Germany) including downsampling to 512 Hz for the purpose of data reduction, correcting for horizontal and vertical eye movements using an independent component analysis (Jung et al. 2000), and transforming to the average reference (Lehmann and Skrandies 1980). Trials with artifacts exceeding ±100 μV in any channel were automatically rejected. The remaining trials were epoched from −1100 to 1500 ms. Evoked potentials (EPs) were computed by averaging the epochs. Single-trial data as well as EPs were exported for subsequent processing to Matlab (The Mathworks, Natick, MA).

Time–frequency analyses were performed in Matlab using custom programming on the basis of standard mathematical and signal analysis functions. To compute time–frequency representations (TFRs), we applied a single-trial Hamming tapered, moving window short time Fast Fourier Transformation. The window had a length of 100 data points, was padded with zeros up to 512 data points, and was shifted for 1 data point. Hence, frequency resolution was 1 Hz and temporal resolution was 1/512 s. For each trial and electrode, the baseline corrected TFRs were computed and transformed into percent signal change with respect to the respective baseline from −1000 to 0 ms.

Multivariate Pattern Analysis

To predict an individual's sensitivity to pain from brain activity, we applied MVPA to time–frequency transformed EEG responses to nociceptive stimuli. To make use of the full single-trial information, we applied a 2-step approach. First, we used MVPA to predict single-trial labels (⩽5, low pain; >5, high pain) from the single-trial EEG responses. Second, we applied a voting-based approach to predict an individual's sensitivity to pain (pain sensitive or pain insensitive) from the proportion of low pain and high pain trials. If more high pain trials than low pain trials were predicted the individual was classified as pain sensitive and vice versa. The MVPA was performed separately for each electrode. Importantly, we pursued a cross-subject approach, that is, the classifier was trained on the data of 22 subjects and then applied to a 23rd subject by using the leave-one-out cross-validation method.

Specifically, we used an MVPA combining feature selection techniques with a support vector machine (SVM). We applied the SVM implementation of WEKA software (Hall et al. 2009). The exceptional high dimensionality of the data was reduced by applying Information Gain feature selection (Hall and Holmes 2003). This technique selects the most relevant features of the data by measuring the information gain with respect to the entropy (H) of a class before and after observing the feature:

$$\mathrm{InfoGain}(\mathrm{Class}, \mathrm{Feature}) = \mathrm{H}(\mathrm{Class}) - \mathrm{H}(\mathrm{Class}|\mathrm{Feature}).$$

Within WEKA software, we applied the SVM algorithm by Platt (Platt 1998) which has the capacity to find the largest margin hyperplane separating the training data. A larger margin allows for a better generalization of the object properties. Furthermore, we used a linear SVM kernel which permits a direct interpretation of the weight vector as class separating information. Hence, the support vector weights allow to directly visualize the predictive value of each feature.

Significance of classification accuracy was assessed by computing 95% confidence intervals of classification accuracy using the efficient-score method (Newcombe 1998). In particular, we applied the Wilson procedure with continuity correction to the first step classification of single trials (low pain vs. high pain, $N = 1275$) as well as to the second step classification of an individual's pain sensitivity (pain sensitive vs. pain insensitive, $N = 23$). In addition, permutation statistics were performed for the classification of pain sensitivity. To this end, each trial was randomly labeled high pain or low pain. The classifier was trained on the randomly labeled trials and the resulting classification of the individual's pain sensitivities was determined. This procedure was repeated 1000 times and the distribution of classifications was compared with the classification based on the real data. Permutation statistics were focused on selected electrodes with high classification accuracy (Cz, FCz).

Furthermore, we compared the predictive value of the single-trial TFR approach with additional approaches which do not take into account the temporal–spectral pattern of single-trial responses. To this end, the SVM was also trained with the averaged TFR, the averaged EP, and the single-trial raw data of 22 subjects. Again, the classifier was then applied to the 23rd subject. This procedure was performed for each electrode separately. Classification accuracy of these approaches to the initial approach was compared by using the nonparametric Wilcoxon signed-rank test (Pereira et al. 2009). Specifically, accuracy of all electrodes for one approach represented one sample and was compared with accuracy of all electrodes for another approach as another sample.

Moreover, topographical maps were created which show the classification accuracy of each electrode across the scalp. In addition, SVM discrimination TFRs were calculated which show the support vector weights, that is, the predictive value as a function of time and frequency.

Results

Stimuli elicited moderately painful sensations with a group mean pain intensity of 4.9. However, pain intensity elicited by the repeated application of identical stimuli varied substantially across (Lanier 1943; Coghill et al. 2003) and within (Rosier et al. 2002; Quiton and Greenspan 2008) individuals (Fig. 1). We aimed to predict the interindividual differences in the perception of identical stimuli from brain activity. We therefore labeled each subject as pain insensitive or pain sensitive based on their ratings of the painful stimuli. Specifically, subjects who rated more often ⩽5 than >5 were labeled pain insensitive and subjects who rated more often >5 than ⩽5 were labeled pain sensitive. In a next step, we aimed to predict these true labels from brain activity.

During the experiment, brain activity was recorded from 64 EEG electrodes. To assess the temporal–spectral pattern of different neuronal responses to pain, we computed TFRs of pain-related neuronal responses. TFRs show neuronal activity as a function of time and frequency and include phase-locked and nonphase-locked neuronal responses at different frequencies. The group mean TFR at exemplary vertex electrode FCz confirms a pattern of 3 pain-related neuronal responses (Fig. 2*A*): evoked responses with a maximum at theta frequencies below 10 Hz and at latencies between 150 and 350 ms (Garcia-Larrea et al. 2003; Lorenz and Garcia-Larrea 2003), gamma responses around 80 Hz at latencies between 150 and 350 ms (Gross et al. 2007; Hauck et al. 2007), and a decrease of alpha activity around 10 Hz starting at about 500 ms after stimulus application (Mouraux et al. 2003; Ploner et al. 2006).

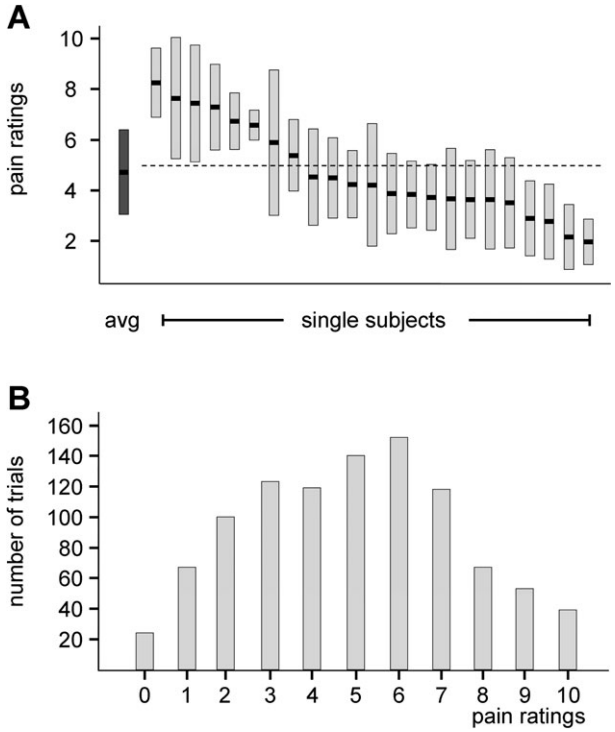

Figure 1. Behavioral data. (*A*) Individual pain ratings (light gray, mean ± standard deviations) and the mean pain rating across all subjects (black, mean ± standard deviation). Subjects with a mean pain rating of >5 or ≤5 (dashed horizontal line) were labeled pain sensitive or pain insensitive, respectively. (*B*) Distribution of single-trial pain ratings.

To predict an individual's pain sensitivity from pain-related EEG responses, we applied an MVPA using a SVM classifier. To make use of the information of all single trials, we pursued a 2-step approach. First, the classifier was trained to predict the perception of single trials. Second, we inferred an individual's sensitivity to pain from the predicted perception of the single trials. For the first step, we assigned true labels to each single trial (low pain, rating ≤ 5; high pain, rating > 5) corresponding to the true labels of the subjects (see above). The classifier was trained on the single-trial TFRs of 22 subjects and applied to predict the single-trial labels (low pain vs. high pain) of the 23rd subject. In a second step, we inferred an individual's pain sensitivity from the individual proportion of low pain and high pain trials. Prediction accuracy was assessed by comparing the predicted pain sensitivity based on brain activity with the individual's true pain sensitivity based on the pain ratings. The procedure was performed for each electrode. The results show that our approach allows for decoding an individual's sensitivity to pain with a maximum accuracy of 83% (19 of 23 subjects). Maximum accuracy was accomplished when using the EEG data of each of 4 electrodes mainly at central locations (Fig. 2*B*, left; Table 1). Statistical testing confirmed that this accuracy was higher than chance (50%) (95% confidence interval, 73–93%; permutation tests at electrodes Cz and FCz, $P < 0.001$). Accuracy of classification of single trials (low pain vs. high pain, electrode FCz) across subjects was 62% (95% confidence interval, 59–65%) which was also significantly higher than chance (50%).

Next, we investigated which pain-related neuronal responses contribute to the classification accuracy. We therefore calculated SVM discrimination TFRs which do not show neuronal activity but the predictive value of neuronal activity as a function of time and frequency. Results show that the evoked theta and the gamma response but not the late alpha response contribute to the classification of the individual sensitivity to pain (Fig. 2*B*, middle).

We finally compared our single-trial TFR-based analysis with approaches which do not take single trials and/or the temporal–spectral pattern of responses at different frequencies into account. We therefore averaged the TFRs across trials for each electrode and subject. These averaged TFRs assess the temporal–spectral pattern of neuronal responses to pain but do not include the single-trial information. Classification of subjects based on this approach shows a maximum accuracy of 78% at a single electrode (Fig. 3*A*). Next, we based the classification on the single-trial raw EEG data which include the single-trial information but do not assess the temporal–spectral pattern of neuronal responses. The results show a maximum classification accuracy of 78% at one left hemispheric electrode (Fig. 3*B*). Finally, we calculated the EP by averaging the EEG data across trials for each electrode and subject. The averaged EP does neither assess the temporal–spectral pattern of information nor the single-trial information. This approach resulted in a maximum classification accuracy of 78% at 3 left hemispheric electrodes (Fig. 3*C*). Statistical comparisons confirmed that our initial approach had a significantly higher predictive value than the other approaches (all $P < 0.001$, Wilcoxon signed-rank tests, Table 2).

In summary, our results show that the multivariate assessment of the temporal–spectral pattern of single-trial EEG responses to pain allows for significant predictions of an individual's sensitivity to pain from brain activity.

Discussion

Here, we aimed to predict an individual's sensitivity to pain from brain activity. We repeatedly applied identical painful stimuli to healthy human subjects and recorded neuronal responses to pain by using EEG. We applied a multivariate analysis to the EEG data to predict an individual's sensitivity to pain from the temporal–spectral pattern of single-trial neuronal responses to nociceptive stimuli. The results show that this approach allows for predicting an individual's pain sensitivity with an accuracy of 83%. Intriguingly, we pursued a cross-subject approach in which the prediction was based on a classifier trained on independent data from other individuals. Our findings may thus help to establish a much sought-after objective neuronal marker of an individual's sensitivity to pain (Borsook et al. 2010; Tracey 2011).

Our results corroborate a substantial interindividual variability in the perception of identical painful stimuli. Differences in sensitivity are observed in all sensory modalities but particularly apply to the perception of pain (Lanier 1943; Coghill et al. 2003; Nielsen et al. 2009) where the individual sensitivity influences future pain experiences and responses to analgesic treatment (Edwards 2005; Nielsen et al. 2009). Variations in pain sensitivity may be caused at any stage in pain processing from the skin to the brain. Mechanisms contributing to interindividual differences in pain sensitivity include genetic, environmental, psychological, and cognitive factors (Nielsen et al. 2009; Coghill 2010). However, regardless of its origin and the underlying mechanisms, perceptual variation should be

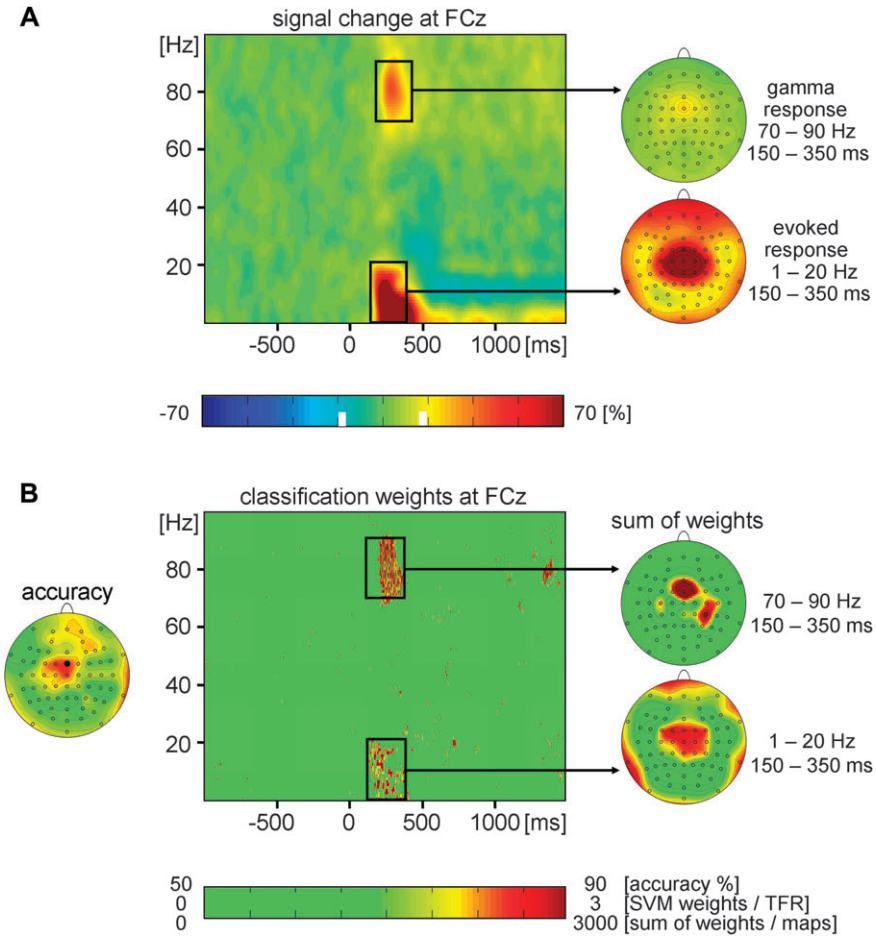

Figure 2. (*A*) Neuronal responses to painful stimuli. TFR of neuronal activity at electrode FCz coded as percent signal change with respect to a prestimulus baseline (left). The group mean TFR has been averaged across trials and subjects. Group mean topography of gamma and evoked responses coded as percent signal change with respect to a prestimulus baseline (right). (*B*) Decoding an individual's sensitivity to pain. Topography of classification accuracy for the single-trial TFR data (left). The SVM discrimination TFR at electrode FCz shows the classification weight, that is, the predictive value as a function of time and frequency (middle). Topography of classification weights for the gamma response and the evoked theta response (right).

Table 1

Classification accuracy, sensitivity, and specificity of different approaches to decode an individual's sensitivity to pain

	Single-trial TFR	Mean TFR	Single-trial raw EEG	Averaged EP
FC1	0.83/0.50/1.00	0.57/0.00/0.87	0.65/0.22/0.93	0.65/0.00/0.83
FC3	0.78/0.38/1.00	0.61/0.13/0.87	0.70/0.22/1.00	0.74/0.00/0.94
FCz	0.83/0.50/1.00	0.65/0.25/0.87	0.70/0.33/0.93	0.13/0.13/0.00
FC2	0.78/0.38/1.00	0.65/0.25/0.87	0.70/0.33/0.93	0.57/0.00/0.72
FC4	0.70/0.25/0.93	0.57/0.13/0.80	0.65/0.11/1.00	0.65/0.00/0.83
C1	0.78/0.50/0.93	0.61/0.25/0.80	0.78/0.44/1.00	0.65/0.00/0.83
C3	0.78/0.50/0.93	0.61/0.00/0.93	0.74/0.33/1.00	0.70/0.20/0.83
Cz	0.83/0.50/1.00	0.52/0.13/0.73	0.70/0.44/0.86	0.70/0.00/0.89
C2	0.74/0.38/0.93	0.61/0.38/0.73	0.74/0.44/0.93	0.57/0.00/0.72
C4	0.74/0.25/1.00	0.52/0.00/0.80	0.70/0.22/1.00	0.57/0.00/0.72
CP1	0.78/0.38/1.00	0.48/0.13/0.67	0.70/0.33/0.93	0.70/0.00/0.89
CP3	0.74/0.38/0.93	0.70/0.13/1.00	0.70/0.33/0.93	0.78/0.40/0.89
CPz	0.74/0.38/0.93	0.57/0.13/0.80	0.70/0.33/0.93	0.61/0.00/0.78
CP2	0.74/0.38/0.93	0.57/0.00/0.87	0.70/0.33/0.93	0.74/0.20/0.89
CP4	0.65/0.25/0.87	0.61/0.13/0.87	0.57/0.11/0.86	0.52/0.00/0.67

Note: For ease of readability, results from a selection of 15 EEG electrodes from central locations are shown.

finally reflected in the neural activity of the brain which ultimately determines the perception of pain. Correspondingly, an fMRI study indicated that pain-related BOLD responses in somatosensory, anterior cingulate, and prefrontal cortices reflect differences in the sensitivity to pain (Coghill et al. 2003). An EEG study showed that pain sensitivity correlates with amplitudes of evoked responses (Iannetti et al. 2005). Our study complements and extends these studies by revealing that different neuronal responses do not only correlate with the sensitivity to pain but that the multivariate assessment of the temporal–spectral pattern of pain-related neuronal responses allows for predicting an individual's sensitivity to pain from brain activity.

Specifically, our results show that the prediction of an individual's sensitivity to pain depends on the pattern of pain-evoked responses at around 8 Hz and pain-induced gamma oscillations at about 80 Hz. This approach yielded significantly higher classification accuracy than approaches which do not take the temporal–spectral pattern of single-trial responses into account. We specifically compared our approach with an approach which is based on an individual's averaged EP. As the latter approach includes only a single time series it represents virtually a univariate analysis. Moreover, our approach was also more powerful than an approach based on an individual's averaged TFR which indicates that single trials contain information which goes beyond the information of an average.

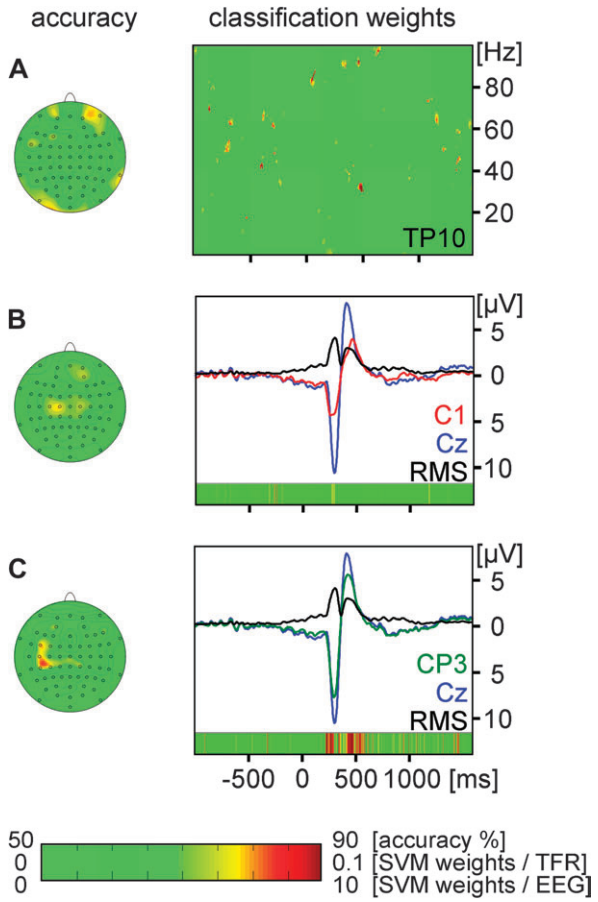

Figure 3. Decoding an individual's sensitivity to pain based on (*A*) the averaged TFR, (*B*) the single-trial raw EEG data, and (*C*) the averaged EP. Left panels show topographies of classification accuracy. Right panels show SVM classification weights color coded as a function of time and frequency (*A*) and as a function of time (*B*,*C*). (*A*) and (*C*) also include time courses of signals at selected electrodes and root mean squares (RMSs) of all electrodes.

Table 2
Statistical comparisons of different approaches to decode an individual's sensitivity to pain

	Single-trial TFR	Averaged TFR	Single-trial raw EEG
Averaged TFR	$z = -6.53$ $P < 0.001$	—	—
Single-trial raw EEG	$z = -6.57$ $P < 0.001$	$z = -4.59$ $P < 0.001$	—
Averaged EP	$z = -6.66$ $P < 0.001$	$z = -4.82$ $P < 0.001$	$z = -5.96$ $P < 0.001$

Note: Wilcoxon signed-rank tests were used to compare accuracy of the different approaches. Specifically, accuracies of all electrodes for one approach represented one sample and were compared with accuracies of all electrodes for another approach as another sample.

Our results, thus, reveal that the cerebral representation of pain is inherently multivariate and that the temporal–spectral pattern of neuronal responses to pain provides crucial information about the perception of pain. Consequently, multivariate approaches which jointly assess temporal–spectral and/or spatial patterns of neuronal responses appear particularly promising to further the understanding of the cerebral representation of pain.

Our approach builds upon recent MVPA of fMRI (Haynes and Rees 2006; Norman et al. 2006) and electrophysiological (Lotte et al. 2007) data which are intended to identify patterns of brain activity that differentiate between mental states (e.g., Haxby et al. 2001; Haynes and Rees 2005; Formisano et al. 2008; Kay et al. 2008). A recent fMRI study used MVPA to predict 3 objectively different levels of thermal stimulation from the spatial pattern of brain activity (Marquand et al. 2010). Here, we go beyond that study and most other brain reading applications (for exceptions, see Mourao-Miranda et al. 2005; Shinkareva et al. 2008; Poldrack et al. 2009) by applying a cross-subject approach. To this end, the classifier was trained on a group of subjects and then applied to another subject to predict the subject's sensitivity to pain. Moreover, we did not distinguish between objectively different intensities of thermal stimuli but we predicted interindividual differences in the perception of identical stimuli. In addition, we used EEG recordings to assess the temporal–spectral rather than the spatial pattern of single-trial responses to pain. The cross-subject approach, the prediction of subjective differences in the perception of identical stimuli, and the use of rather cheap and simple EEG recordings may represent a step further toward translation of brain reading approaches into practical applications.

However, several limitations of the present approach should be noted. First, we used a simplified dichotomous model of pain sensitivity. Such a simplified categorical model appears robust and reasonable as a first step toward practical applications but does not necessarily generalize to all conditions and subjects. Second, the relationship between pain perception and neuronal responses is not fully stable. Specifically, short and constant ISIs can disrupt the relationship between amplitudes of neuronal responses and pain perception (Iannetti et al. 2008). Our approach thus applies only to sufficiently long and varied ISIs (8–12 s). Moreover, pain ratings do not allow to disentangle perception from other evaluation processes. Prior to practical applications it should, thus, be investigated to what an extent the approach is susceptible to other evaluation processes or simulation. Third, our assessment refers to the momentary sensitivity to pain which can be influenced by a broad variety of internal and external factors including skin temperature. Future studies should therefore define the experimental conditions as thoroughly as possible including assessments of skin temperature. Fourth, we used a linear SVM to decode pain sensitivity. This classifier is often used in brain reading studies but other linear and nonlinear classifiers may be equally or even more powerful (for a discussion of different classifiers, see Mur et al. 2009; Pereira et al. 2009). Fifth, we only assessed the temporal–spectral but not the spatial pattern of responses and, as most previous MVPA of brain activity, we performed a binary classification. The integration of temporal–spectral information with spatial information assessed by a source analysis of EEG or even by fMRI could potentially further improve the multivariate assessment of pain sensitivity. However, integration of spatial information and classification of multiple classes would be computationally highly demanding. For example, a source based approach to the EEG data even when using a large voxel size of 7 mm would multiply the data by the factor 100 as compared with the present electrode-based approach.

Intriguingly, our approach is based on a very simple experiment so that the data can potentially be recorded during a few minutes from a single EEG electrode. Our observations may thus be instrumental in establishing a simple neuronal marker of pain perception which could determine an individual's

sensitivity to pain in situations where verbal report is not available or reliable, for example, in critically ill or demented patients or patients suspected of malingering. In these patients as well as in patients with disorders of consciousness, the characterization of an individual's pain sensitivity could help to optimize general care and analgesic treatment. Our approach could thereby help to improve the prevention, diagnosis, and treatment of pain with implications for health care (Borsook et al. 2010; Tracey 2011) and the legal system (Miller 2009).

Funding

Deutsche Forschungsgemeinschaft (PL 321/6-1); Studienstiftung des Deutschen Volkes.

Notes

Conflict of Interest: None declared.

References

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 9:463–484.

Borsook D, Sava S, Becerra L. 2010. The pain imaging revolution: advancing pain into the 21st century. Neuroscientist. 16:171–185.

Coghill RC. 2010. Individual differences in the subjective experience of pain: new insights into mechanisms and models. Headache. 50: 1531–1535.

Coghill RC, McHaffie JG, Yen YF. 2003. Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci U S A. 100:8538–8542.

Edwards RR. 2005. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology. 65:437–443.

Formisano E, De Martino F, Bonte M, Goebel R. 2008. "Who" is saying "what"? Brain-based decoding of human voice and speech. Science. 322:970–973.

Garcia-Larrea L, Frot M, Valeriani M. 2003. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin. 33:279–292.

Gross J, Schnitzler A, Timmermann L, Ploner M. 2007. Gamma oscillations in human primary somatosensory cortex reflect pain perception. PLoS Biol. 5:e133.

Hall M, Frank E, Holmes G, Pfahringer B, Reutemann P, Witten IH. 2009. The WEKA data mining software: an update. SIGKDD Explor. 11:10–18.

Hall MA, Holmes G. 2003. Benchmarking attribute selection techniques for discrete class data mining. IEEE Trans Knowl Data Eng. 15:1437–1447.

Hauck M, Lorenz J, Engel AK. 2007. Attention to painful stimulation enhances gamma-band activity and synchronization in human sensorimotor cortex. J Neurosci. 27:9270–9277.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P. 2001. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science. 293:2425–2430.

Haynes JD, Rees G. 2005. Predicting the stream of consciousness from activity in human visual cortex. Curr Biol. 15:1301–1307.

Haynes JD, Rees G. 2006. Decoding mental states from brain activity in humans. Nat Rev Neurosci. 7:523–534.

Iannetti GD, Hughes NP, Lee MC, Mouraux A. 2008. Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? J Neurophysiol. 100:815–828.

Iannetti GD, Zambreanu L, Cruccu G, Tracey I. 2005. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience. 131:199–208.

Jung TP, Makeig S, Westerfield M, Townsend J, Courchesne E, Sejnowski TJ. 2000. Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects. Clin Neurophysiol. 111:1745–1758.

Kay KN, Naselaris T, Prenger RJ, Gallant JL. 2008. Identifying natural images from human brain activity. Nature. 452:352–355.

Lanier LH. 1943. Variability in the pain threshold. Science. 97:49–50.

Lehmann D, Skrandies W. 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr Clin Neurophysiol. 48:609–621.

Lorenz J, Garcia-Larrea L. 2003. Contribution of attentional and cognitive factors to laser evoked brain potentials. Neurophysiol Clin. 33:293–301.

Lotte F, Congedo M, Lecuyer A, Lamarche F, Arnaldi B. 2007. A review of classification algorithms for EEG-based brain-computer interfaces. J Neural Eng. 4:R1–R13.

Marquand A, Howard M, Brammer M, Chu C, Coen S, Mourao-Miranda J. 2010. Quantitative prediction of subjective pain intensity from whole-brain fMRI data using Gaussian processes. Neuroimage. 49:2178–2189.

Miller G. 2009. Neuroscience. Brain scans of pain raise questions for the law. Science. 323:195.

Mourao-Miranda J, Bokde AL, Born C, Hampel H, Stetter M. 2005. Classifying brain states and determining the discriminating activation patterns: support vector machine on functional MRI data. Neuroimage. 28:980–995.

Mouraux A, Guerit JM, Plaghki L. 2003. Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between A partial partial differential- and C-fibre afferent volleys. Clin Neurophysiol. 114:710–722.

Mur M, Bandettini PA, Kriegeskorte N. 2009. Revealing representational content with pattern-information fMRI—an introductory guide. Soc Cogn Affect Neurosci. 4:101–109.

Newcombe RG. 1998. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 17:857–872.

Nielsen CS, Staud R, Price DD. 2009. Individual differences in pain sensitivity: measurement, causation, and consequences. J Pain. 10:231–237.

Norman KA, Polyn SM, Detre GJ, Haxby JV. 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn Sci. 10:424–430.

Pereira F, Mitchell T, Botvinick M. 2009. Machine learning classifiers and fMRI: a tutorial overview. Neuroimage. 45:S199–S209.

Platt JC. 1998. Fast training of support vector machines using sequential minimal optimization. In: Schölkopf B, Burges CJC, Smola AJ, editors. Advances in kernel methods: support vector learning. Cambridge (MA): MIT Press. p. 185–208.

Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A. 2006. Pain suppresses spontaneous brain rhythms. Cereb Cortex. 16:537–540.

Poldrack RA, Halchenko YO, Hanson SJ. 2009. Decoding the large-scale structure of brain function by classifying mental states across individuals. Psychol Sci. 20:1364–1372.

Quiton RL, Greenspan JD. 2008. Across- and within-session variability of ratings of painful contact heat stimuli. Pain. 137:245–256.

Rosier EM, Iadarola MJ, Coghill RC. 2002. Reproducibility of pain measurement and pain perception. Pain. 98:205–216.

Schulz E, Tiemann L, Schuster T, Gross J, Ploner M. 2011. Neurophysiological coding of traits and states in the perception of pain. Cereb Cortex. 21:2408–2414.

Shinkareva SV, Mason RA, Malave VL, Wang W, Mitchell TM, Just MA. 2008. Using FMRI brain activation to identify cognitive states associated with perception of tools and dwellings. PLoS One. 3:e1394.

Tracey I. 2011. Can neuroimaging studies identify pain endophenotypes in humans? Nat Rev Neurol. 7:173–181.

Tracey I, Mantyh PW. 2007. The cerebral signature for pain perception and its modulation. Neuron. 55:377–391.