Neurophysiological Coding of Traits and States in the Perception of Pain

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Perception is not a simple reflection of sensory information but varies within and between individuals. This applies particularly to the perception of pain, which, in the brain, is associated with neuronal responses at different frequencies. Here, we show how these different neuronal responses subserve interindividual and intraindividual variations in the perception of identical painful stimuli. A time–frequency analysis of single trial electroencephalographic data indicates that pain-related responses in the theta frequency range but not at higher gamma frequencies code for interindividual variations in the perception of pain. In contrast, both pain-related theta and gamma responses provide different and complementary information on intraindividual variations in the pain experience. We conclude that theta responses reflect rather constant physiological and psychological traits of the individual, whereas gamma responses relate to short-term modulations of the individual’s state. These findings reveal how neuronal responses at different frequencies differentially contribute to the translation of sensory information into a subjective percept.

Keywords: brain, EEG, gamma oscillations, pain, perceptual variability

Introduction

Perception is inherently variable, even when sensory information is kept as constant as possible (Fechner 1860; Ashby and Lee 1993; Deco and Romo 2008). This applies particularly to the perception of pain where some individuals perceive a sensory event as painful, whereas others perceive the very same event as not painful at all (Coghill et al. 2003; Nielsen et al. 2005). Moreover, even for the same individual, the perception of similar painful events varies over time (Rosier et al. 2002; Boly et al. 2007; Quilot and Greenspan 2008). These intraindividual and interindividual variations of the pain experience are likely to reflect different aspects of perception and neural processing. Intraindividual variations of pain perception reflect variations of the individual’s state on a short time scale, whereas interindividual variations of perception reflect rather constant physiological and psychological traits of the individual. Together, the constant traits and the variable state of the individual shape the translation of sensory information into a coherent and adaptive percept.

In the brain, the perception of pain is subserved by an extended network of brain areas including somatosensory, insular, cingulate, and prefrontal cortices (Apkarian et al. 2005; Tracey and Mantyh 2007). Neurophysiological studies disclosed that painful stimuli yield different neuronal responses within this network (please note that throughout the manuscript “neuronal responses” and “neuronal activity” refers to correlated synaptic activity caused by postsynaptic potentials as recorded by non-invasive neurophysiological recordings; Lopes da Silva and Van Rotterdam 2005). Numerous investigations recorded pain-evoked potentials, that is, phase-locked averaged pain-related neuronal responses at frequencies below 10 Hz (García-Larrea et al. 2003; Lorenz and García-Larrea 2003). In addition, recent studies revealed pain-induced oscillations at higher gamma (30–100 Hz) frequencies (Gross et al. 2007; Hauck et al. 2007). Other investigations recorded pain-related suppressions of neuronal oscillations at alpha and beta (8–25 Hz) frequencies (Mouraux et al. 2003; Ploner et al. 2006). These responses in different frequency bands partially overlap in time and space (Mouraux et al. 2003; Ploner et al. 2006; Gross et al. 2007; Hauck et al. 2007). However, whether and how these neuronal responses relate to the individual’s traits and states and thereby differentially contribute to the translation of sensory information into the subjective experience of pain is largely unknown.

In a simple experiment, we therefore investigated the relationship between different pain-related neuronal responses and intraindividual and interindividual variations in the subjective experience of pain. We took advantage of the variability in perception of identical stimuli (Ashby and Lee 1993; Deco and Romo 2008) and related variations in pain perception to electroencephalographic (EEG) data. A time–frequency analysis of single trial EEG data allows for the differentiation of pain-related neuronal responses at various frequencies. We hypothesized that the different neuronal responses differentially contribute to the translation of sensory information into the perception of pain. Since neuronal gamma oscillations have been implicated in contextual short-term modulations of sensory processing (Salinas and Sejnowski 2001; Fries 2009), we speculated that pain-induced gamma responses would be particularly related to intraindividual variations in the perception of pain, whereas rather constant aspects of pain perception, as reflected by interindividual variations in the pain experience, would be related to pain-evoked responses in the theta range.

Materials and Methods

Eighteen healthy human subjects participated in a simple experiment, where 60 brief painful laser stimuli of constant energy were delivered to the dorsum of the right hand (Fig. 1A). Three seconds after each stimulus, the subjects were prompted to verbally rate the perceived pain intensity on a numerical rating scale between 0 (no pain) and 10 (maximum pain intensity they are willing to tolerate during the experiment).

Subjects

Eight male and 10 female subjects with a mean age of 25 years (20–31 years) participated in the study. Informed consent was given by all...
to the dorsum of the right hand (Fig. 1). Sixty painful cutaneous laser stimuli of equal intensity were delivered.

Paradigm

The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

Sixty painful cutaneous laser stimuli of identical intensity were delivered to the dorsum of the right hand (Fig. 1A). Cutaneous laser stimuli selectively activate nociceptive afferents without concomitant activation of tactile afferents (Treede 2003). The laser device was a Nd:YAP laser (Electronical Engineering) 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 sensations. Distance pins helped to keep the distance of the hand piece of the laser device to the skin constant without touching the skin. Stimulation site was slightly changed after each stimulus. Interstimulus intervals 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). Specifically, subjects were told that "10" indicates the maximum intensity they are willing to tolerate during the experiment. Prior to the experiment, subjects were informed that pain intensity may vary during the experiment. However, all laser stimuli were of equal intensity.

EEG Recordings and Analysis

EEG data were recorded using an electrode cap (FMS). 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, C1/2/3/5/6, CP1/2/3/4/5, TP7/8/9/10, P5/6, PO1/2/9/10 (American Electroencephalographic Society 1991), 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 (Ferree et al. 2000).

The raw EEG data were preprocessed in Vision Analyzer software (Brain Products) including downsampling to 512 Hz, 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 and exported to Matlab (The Mathworks).

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 (FFT). 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.

First, we determined pain-related changes in neuronal activity. On a single trial basis, TFRs were computed and transformed into percent signal change values with respect to the single trial baseline from –1000 to 0 ms. For each subject and electrode, the baseline corrected single trial TFRs were averaged across trials. For each electrode, whole group TFRs were calculated by averaging the individual TFRs across subjects. These grand mean TFRs showed strongest neuronal responses to painful stimuli in the theta (3–8 Hz, 150–350 ms), gamma (76–86 Hz, 150–350 ms), and alpha frequency bands (8–15 Hz, 500–700 ms). Statistical significance of these responses was assessed by calculating Bonferroni corrected paired t-test on the neuronal activity in the aforementioned time-frequency windows and the respective baseline (–1000 to 0 ms) for each electrode. To keep baseline values above zero, the statistical analysis was based on the averaged TFRs without any baseline correction.

Next, we addressed intraindividual variations of neuronal responses and pain perception. We therefore applied linear mixed models (LMM) to the data. The LMM approach reflects the structure of repeated data and takes correlation of measurements within the same subject into account. The fixed effect parameters were computed to assess intraindividual (conditional) dependence of neuronal responses on pain perception. LMM were calculated for each data point of the baseline corrected single trial TFRs (1232 time × 100 frequency steps for each of the 65 electrodes). This analysis yields group mean TFRs, which do not show neuronal activity but the relationship between neuronal activity and pain perception as a function of time and frequency. To control for type I error, false discovery rate (FDR) correction across electrodes and the whole time-frequency range of the TFRs was performed (Genovese et al. 2002).

To further analyze the contribution of the different neuronal responses to intraindividual variability of pain perception, we defined theta, gamma, and alpha responses as mean activity from the aforementioned time-frequency windows. Responses were defined from electrodes Cz, FCz, and CP4, respectively, since these electrodes showed strongest responses. We then determined the contribution of each response type to the pain experience by applying LMM with 1) theta responses, 2) gamma responses, 3) alpha responses, 4) theta and gamma responses, 5) theta and alpha responses, 6) alpha and gamma responses, and 7) all 3 responses as independent variables. To determine the explanatory value of the models, we calculated the Bayesian information criterion (BIC) for each model, where lower BIC values indicate a better model fit. A bootstrap-sampling approach was used to statistically compare the models (Efroim and Tibshirani 1993). For each model, the BIC values from 1000 new data sets generated from our original data set by simple random sampling (with replacement) were computed. Two models were considered to have significantly different explanatory value if the 95% bootstrap confidence interval for the difference in corresponding BIC values did not include 0 value.

We, next, specifically investigated the interindividual variability of neuronal responses and pain perception. We therefore performed regression analyses with each individual's mean pain rating as dependent variable and the individual mean theta, gamma, and/or alpha response amplitudes as independent variables. To selectively address interindividual but not intraindividual variations in pain perception, response amplitudes and pain ratings were averaged across trials before the regression analyses were performed. Electrodes and time–frequency windows were the same as for the analysis of the intraindividual variability. To assess the predictive value of the different response types, we compared regression models, where individual means of 1) theta responses, 2) gamma responses, 3) alpha responses, 4) theta and gamma responses, 5) theta and alpha responses, 6) alpha and
gamma responses, and 7) all 3 responses were included as independent variables. The corrected $r^2$ value was used to evaluate the models.

**Results**

**Intraindividual and Interindividual Variability in the Perception of Pain**

Laser stimuli elicited moderately painful pinprick-like sensations with a mean pain intensity of 5.0 across subjects (Fig. 1B). However, pain intensity elicited by the repeated application of identical stimuli varied within and between individuals. A root mean square standard deviation of pain ratings within individuals of 1.9 confirms a substantial intraindividual variability in the perception of pain (Rosier et al. 2002; Boly et al. 2007; Quiton and Greenspan 2008) (Fig. 1B, light gray bars). Furthermore, a standard deviation of mean pain ratings across individuals of 2.1 corroborates a considerable interindividual variability in pain perception (Coghill et al. 2003; Nielsen et al. 2005) (Fig. 1B, dark gray bar).

**Neuronal Responses to Painful Stimuli**

We first aimed to determine neuronal responses to painful stimuli. To this end, TFRs were calculated for each trial and electrode. These TFRs show neuronal activity as a function of time and frequency and include phase-locked as well as non-phase-locked neuronal responses. The group mean TFR at exemplary vertex electrode FCz shows that the brief painful stimuli yielded 3 different neuronal responses at latencies between 150 and 1000 ms after stimulus application (Fig. 2).

First, we found a strong increase of neuronal activity (162% maximum signal change, $P < 0.001$) with a maximum in the theta frequency range (3–8 Hz) at latencies between 150 and 350 ms corresponding to the well-known pain-evoked potential including its N1, N2, and P2 components. Phase locking of theta responses (Supplementary Fig. S1) as well as the topographies of theta responses and evoked responses (Supplementary Fig. S2) corroborate that the theta responses correspond to the pain-evoked potential. Second, we observed a less pronounced increase of neuronal activity (24% maximum signal change, $P < 0.05$) in the gamma frequency band between 70 and 90 Hz at latencies between 150 and 350 ms, which confirms recent descriptions of pain-induced gamma oscillations in magnetoencephalographic (MEG) recordings (Gross et al. 2007; Hauck et al. 2007). Third, we identified a pain-related decrease in neuronal activity (~32% maximum signal change; $P < 0.05$) around 10 Hz starting at about 500 ms after stimulus application, which corresponds to a suppression of neuronal oscillations in the alpha frequency band (Mouraux et al. 2003; Ploner et al. 2006). The topographical maps of the different pain-related neuronal responses show that theta and gamma responses are strongest at vertex electrodes, whereas the alpha suppression is strongest at left parietooccipital electrodes. Thus, brief painful stimuli yield 3 neuronal responses, which partially overlap in time and space.

**Intraindividual Variability in Neuronal Responses and Pain Perception**

We next aimed to disentangle how the 3 different neuronal response types contribute to intraindividual and interindividual variations in the perception of pain. We first addressed the intraindividual variability in the perception of pain. We therefore related single trial neuronal responses to single trial pain ratings by calculating LMM for each data point of the single trial TFRs. This yields TFRs, which do not show neuronal activity but the relationship between neuronal activity and pain perception as a function of time and frequency. Figure 3A shows the resulting TFR at exemplary electrode FCz. Please note that this analysis selectively addresses intraindividual but

![Figure 3. Intraindividual variability in neuronal responses and pain perception.](image)
not interindividual variability in neuronal responses and pain perception. We observed a positive relationship between neuronal activity in the theta frequency band (150–350 ms) and pain perception ($t_{\text{max}} = 9.4, P < 0.05$). We further found a positive relationship between neuronal activity in the gamma frequency band (150–350 ms) and pain perception ($t_{\text{max}} = 6.8, P < 0.05$). Finally, the TFR shows a negative relationship between neuronal activity in the alpha frequency band (500–700 ms) and the perception of pain ($t_{\text{max}} = -6.3, P > 0.05$, all FDR corrected across electrodes, time, and frequency). Thus, on a single trial level, theta, gamma, and alpha responses are related to intraindividual variations in the subjective experience of pain.

Next, we tested whether the different responses provide similar or complementary information about the subjective experience of pain. We therefore calculated and compared LMM with 1) theta responses, 2) gamma responses, 3) alpha responses, 4) theta and gamma responses, 5) theta and alpha responses, 6) alpha and gamma responses, and 7) all 3 responses as independent variables. We compared the explanatory value of the models by calculating the BIC for each model. The model 4 that includes theta and gamma response had a significantly higher explanatory value than models 1–3 that include theta, gamma, or alpha responses alone (Fig. 3B and Supplementary Fig. S3). Intriguingly, as theta and gamma responses together explain the intraindividual variability of pain perception significantly better than each response alone, both responses provide different and complementary information about the pain experience. In contrast, additional inclusion of alpha responses into the model did not significantly improve the explanatory value. Alpha responses do, thus, not add significant information on the perception of pain but may rather echo the preceding theta and/or gamma responses. These results reveal that pain-related theta and gamma responses provide complementary information about intraindividual short-term variations in the perception of pain.

**Interindividual Variability in Neuronal Responses and Pain Perception**

Finally, we addressed the interindividual variability in the perception of pain. To this end, we performed regression analyses with each individual's mean pain rating as dependent variable and the individual mean theta, gamma, and/or alpha response amplitudes as independent variables. This analysis selectively addresses interindividual but not intraindividual variations in pain perception since response amplitudes and pain ratings were averaged across trials prior to the regression analyses (Bland and Altman 1995). To assess the predictive value of the different response types, we compared regression models, where individual means of 1) theta responses, 2) gamma responses, 3) alpha responses, 4) theta and gamma responses, 5) theta and alpha responses, 6) alpha and gamma responses, and 7) all 3 responses were included as independent variables. We found that the individual mean theta response amplitude significantly predicted the individual mean pain intensity (model 1, $r = 0.48$, $P < 0.05$, Fig. 4). In contrast, there was neither a significant influence of gamma nor for alpha responses on pain intensity (models 2 and 3, $r = 0.27$ and $r = -0.16$, $P > 0.05$). Correspondingly, regression analyses with 2 or 3 responses (models 4–7) as independent variables did not significantly improve the model as compared with theta responses alone (Table 1). These results indicate that theta responses but not gamma or alpha responses significantly predict interindividual variations in the subjective experience of pain.

**Discussion**

Here, we investigated how different neuronal responses in the human brain differentially subserve the perception of pain. We therefore related interindividual and intraindividual variations in the perception of identical painful stimuli to different neuronal response types. Our time–frequency analysis of EEG data shows that pain-evoked theta responses but not pain-induced gamma or alpha responses code for interindividual variations in the pain experience, which are likely to reflect constant physiological and psychological traits of the individual. In contrast, a single trial analysis reveals that both pain-evoked theta responses and pain-induced gamma oscillations provide different and complementary information on intraindividual variations in pain perception, which are likely to reflect short-term changes in the individual’s state.

Pain is a particularly variable sensory experience, which therefore lends itself to investigate how sensory information is translated into a subjective percept. In our study, we confirmed that the perception of similar painful stimuli varies substantially within and between individuals. This finding is in line with previous studies showing remarkable interindividual (Rosier et al. 2002; Quiton and Greenspan 2008) and intraindividual (Rosier et al. 2002; Quiton and Greenspan 2008) variations in the pain experience. In principle, perceptual variability can be due to differences in the peripheral and/or central processing of sensory events (Ashby and Lee 1993). Peripheral factors like skin thickness and receptor density are likely to contribute to the observed variability in the present study, the more so as the location of thermal stimuli had to be slightly changed after each stimulus to avoid tissue damage. However, the observation that the cerebral representations of interindividual and intraindividual variations in the pain experience differ fundamentally confirms a significant contribution of central factors to interindividual (Coghill et al. 2003; Zubieta et al. 2003; Nielsen et al. 2005) and intraindividual perceptual variability (MacDonald et al. 2006; Deco and Romo 2008).

Importantly, interindividual and intraindividual variations in the pain experience represent different aspects of pain.

![Figure 4. Interindividual variability in neuronal responses and pain perception. Correlation between the mean individual pain intensity and the mean amplitudes of theta responses at Cz, alpha responses at CP4, and gamma responses at FCz.](image-url)
Interindividual variability in neuronal responses and pain perception

We observed 3 different neuronal responses associated with the experience of pain. Painful stimuli elicited increases in neuronal activity in the theta and in the gamma frequency band as well as a decrease in the alpha band. The pain-related theta response corresponds to the well-known pain-evoked potential, which has been extensively analyzed in the time (Garcia-Larrea et al. 2003; Lorenz and Garcia-Larrea 2003) and frequency domain (Mouraux and Plaghi 2004; Iannetti et al. 2008). We further found that pain induces gamma responses, which corroborates recent MEG observations of pain-induced gamma oscillations, which temporally and spatially overlap with the pain-evoked potentials/fields (Gross et al. 2007; Hauck et al. 2007). Latencies and frequencies of gamma responses correspond well to previous investigations (Gross et al. 2007; Hauck et al. 2007). However, in the present EEG study, gamma responses were strongest at central electrodes, whereas in previous MEG studies gamma responses were lateralized to the contralateral hemisphere (Gross et al. 2007; Hauck et al. 2007). This discrepancy may be due to different recording technologies. EEG signals are influenced by the CSF, the skull, and the scalp, whereas MEG signals are not. Moreover, MEG is mostly sensitive to tangential currents, whereas EEG also detects radial currents. Thus, the topography of EEG and MEG signals can differ substantially which complicates or even hinders a direct comparison of topographies obtained by both methods. The focal spatial and spectral distribution of the gamma responses with a maximum at frontocentral electrodes argues against the possibility that the responses are due to muscle activity or miniature saccades which can yield spatially and spectrally broad gamma power increases with a maximum at peripheral (Goncharova et al. 2003) and parietooccipital (Yuval-Greenberg et al. 2008) electrodes, respectively. Moreover, the theta and gamma responses were succeeded by a pain-related suppression of neuronal activity in the alpha band. This finding confirms previous investigations showing a pain-induced suppression of spontaneous neuronal oscillations in the alpha frequency band with later latencies than pain-evoked potentials and pain-induced gamma oscillations but with a partial spatial overlap with these responses (Mouraux et al. 2003; Ploner et al. 2006). Taken together, these results provide a synopsis of the variety of spatially and temporally partially overlapping pain-related neuronal responses in the human brain.

In the present study, we related interindividual and intraindividual variations in the pain experience to the variability in neuronal responses to pain. Our results disclose that pain-evoked theta responses, that is, pain-evoked potentials, and pain-induced gamma oscillations differentially contribute to interindividual and intraindividual variations in the pain experience.

We found that the interindividual variability of pain perception correlates with the amplitudes of pain-evoked theta responses. This result corroborates previous observations of an association between the individual sensitivity to pain and pain-evoked potentials (Iannetti et al. 2005). Thus, pain-evoked theta responses but not pain-induced gamma and alpha responses relate to the individual baseline sensitivity to pain which is shaped by rather constant physiological and psychological traits of the individual. As the present study was focused on the analysis of the EEG data, we did not perform a detailed profiling of the individual’s physiological and psychological traits. The detailed characterization of pain-relevant traits and their relationship to pain-related neuronal responses remains, thus, to be performed in future studies.

We further observed that intraindividual variations in the pain experience are significantly correlated with both theta and gamma responses. These relationships between pain perception and neuronal responses applied to stimuli, which were well in the painful range. In a previous study, perceptual differences between very weak stimuli, which were perceived either as painful or as not painful (Gross et al. 2007) were
coded by gamma responses only. Evoked responses may thus code for intraindividual perceptual variations only in the painful range. Intriguingly, the 2 response types provide different and complementary information on intraindividual short-term variations in the perception of pain, whereas alpha responses do not contain additional information. Centrally, short-term variations in perception are shaped by top-down influences from higher order processing stages (Gilbert and Sigman 2007) and/or changes in the intrinsic neural activity of different functional systems of the brain (Super et al. 2003; de Lafuente and Romo 2005; Sapir et al. 2005; Hesselmann et al. 2008). Since gamma oscillations have been implicated in the top-down mediated control of sensory processing (Salinas and Sejnowski 2001; Fries 2009), we hypothesize that pain-induced gamma oscillations represent a neural substrate of short-term modulations of pain processing at early processing stages. Thereby, gamma oscillations may significantly affect further processing of painful events at higher processing stages beyond unimodal sensory cortices (Salinas and Sejnowski 2001; Fries 2009). Behaviorally, short-term variations in pain sensitivity may be instrumental for the maintenance of behavioral flexibility, which applies particularly to the perception of pain, which imposes a strong behavioral drive on the individual (Melzack and Casey 1968). These short-term variations in the perception of pain as reflected by pain-induced gamma oscillations probably superimpose on rather constant aspects of pain perception, which are represented by pain-evoked theta responses.

In summary, the present study shows that different neuronal responses to a sensory event represent complementary steps in the translation of sensory information into a subjective percept, which is flexibly shaped by constant traits and the variable state of the individual. Our time–frequency analysis of EEG data thus provides basic insights in the functional significance of different neuronal response types and how these neuronal responses shape a variable and adaptive sensory experience. Abnormalities of the translation from sensory information into a percept may yield dysbalances of perception like chronic pain, which often represents a percept without adequate sensory information. Moreover, abnormal increases of intraindividual behavioral variability have been linked to neuropsychiatric disorders (MacDonald et al. 2006). The present findings may thus further the understanding of the cerebral mechanisms of perception in health and disease.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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

Notes
Conflict of Interest : None declared.

References


