Research Paper

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Differential neurophysiological correlates of bottom-up and top-down modulations of pain

Laura Tiemann[a,b,*], Elisabeth S. May[a,b], Martina Postorino[a,b], Enrico Schulz[a,b], Moritz M. Nickel[a,b], Ulrike Bingel[c], Markus Ploner[a,b]

Abstract

The perception of pain is highly variable. It depends on bottom-up-mediated factors like stimulus intensity and top-down-mediated factors like expectations. In the brain, pain is associated with a complex pattern of neuronal responses including evoked potentials and induced responses at alpha and gamma frequencies. Although they all covary with stimulus intensity and pain perception, responses at gamma frequencies can be particularly closely related to the perception of pain. It is, however, unclear whether this association holds true across all types of pain modulation. Here, we used electroencephalography to directly compare bottom-up- and top-down-mediated modulations of pain, which were implemented by changes in stimulus intensity and placebo analgesia, respectively. The results show that stimulus intensity modulated pain-evoked potentials and pain-induced alpha and gamma responses. In contrast, placebo analgesia was associated with changes of evoked potentials, but not of alpha and gamma responses. These findings reveal that pain-related neuronal responses are differentially sensitive to bottom-up and top-down modulations of pain, indicating that they provide complementary information about pain perception. The results further show that pain-induced gamma oscillations do not invariably encode pain perception but may rather represent a marker of sensory processing whose influence on pain perception varies with behavioral context.

Keywords: Electroencephalography, Gamma oscillations, Pain-evoked potentials, Placebo analgesia

1. Introduction

Pain is a highly variable subjective experience, which depends on bottom-up-mediated factors like stimulus intensity and top-down-mediated factors like expectations. In the brain, pain is associated with different neuronal responses originating from an extended network of brain areas.[2,13,38] Traditional time-domain averaging approaches recorded pain-evoked potentials at frequencies below 10 Hz.[12,26] Recent time–frequency analyses of neurophysiological recordings revealed that painful stimuli yield a suppression of neuronal activity at alpha frequencies (8-13 Hz)[30,34] and induce neuronal responses at higher gamma frequencies (30-100 Hz).[15,16,43] The differential functional significance of these responses is not fully understood yet. Whereas they all covary with stimulus intensity and pain perception,[8,14,15] gamma responses are particularly closely related to the perception of pain under certain conditions. These conditions comprise spontaneous fluctuations[15] and attentional modulation[16] of pain as well as stimulus repetition.[43] It is, however, unknown whether this close association between pain perception and gamma responses generalizes to fundamentally different modulations of pain.

Here, we therefore directly compared the functional significance of pain-related brain responses during bottom-up- and top-down-mediated modulations of pain, which were implemented by changes in stimulus intensity and by a placebo analgesia procedure, respectively. We hypothesized that pain-related brain responses would be differentially sensitive to different types of pain modulation. We were further interested to know whether the close relationship between gamma responses and pain perception holds true across fundamentally different modulations of pain.

2. Materials and methods

2.1. Subjects

Twenty healthy human subjects (5 females) with a mean age of 25 years (range, 19-35) were included in the study. These 20 subjects were identified as placebo responders from a total sample of 48 subjects. Placebo responders were defined as subjects with a placebo-induced decrease in pain ratings of ≥20% (see paragraph 2.4). Subjects were recruited through advertisements on bulletin boards of local universities with the understanding that the experiment investigated the neurobiological mechanisms of individual differences in the response to an analgesic cream. Exclusion criteria included a history of neurological or psychiatric disease including chronic or recurrent pain and regular use of medication including analgesics. Procedures were approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] *Department of Neurology, Technische Universität München, Munich, Germany,*
[b] *TUM-Neuroimaging Center, Technische Universität München, Munich, Germany,*
[c] *Department of Neurology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany*

**Corresponding author. Address: Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany. Tel.: +49 89 4140 7664; fax: +49 89 4140 7681. E-mail address: tiemann@lrz.tu-muenchen.de (L. Tiemann).*

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2.2. Stimuli

Painful stimuli were applied to the dorsum of the hand using a Tm: YAG laser (StarMedTec GmbH, Starnberg, Germany) with a wavelength of 1960 nm, a pulse duration of 1 millisecond, and a spot diameter of 5 mm. A distance pin mounted to the handpiece of the laser device ensured a constant distance between skin surface and laser device. The stimulation site was slightly varied after each stimulus to avoid tissue damage. The neuronal responses induced by the laser stimulation will be referred to as pain-evoked potentials and pain-induced responses, respectively, throughout the article.

2.3. Procedure

The experimental procedure consisted of 2 paradigms, which investigated bottom-up and top-down modulations of pain, respectively (**Fig. 1**). To avoid carryover effects from the placebo manipulation to later conditions, paradigms were performed in a fixed order. Before the experiment, participants were informed that the purpose of the study was to investigate the neuronal correlates of interindividual differences in the efficacy of an analgesic cream. The precise instructions included the information that this cream has been shown to be a highly effective analgesic in various previous studies and is frequently used in clinical practice. Subjects were further informed that the effect of the analgesic cream will be compared with that of an inert control cream. We then assessed pain thresholds using the method of limits.[11] For later use during the experiment, we further determined individual low, medium, and high stimulus intensities, matching subjective ratings of 50, 60, and 70 on a numerical rating scale ranging from 0 (no pain) to 100 (maximum tolerable pain). Moreover, we specified sites for later placebo and control cream application (**Fig. 1A**). For this purpose, we outlined the left and right side (or upper and lower half, respectively) of the left hand in green and black color and designated these areas as the later placebo and control sites, respectively. Both the spatial pattern (left/right side vs upper/lower half) and the assignment of the placebo and control sites were counterbalanced across subjects.

The first paradigm investigated bottom-up-mediated modulations of pain, which were implemented by varying the stimulus intensity between low and high intensities (**Fig. 1B**). Participants were told that the purpose of this paradigm was to establish a baseline measure of the individual pain sensitivity. Stimuli were applied in 4 blocks of 20 stimuli each. Each block included 10 low-intensity and 10 high-intensity pain stimuli applied in pseudorandomized sequence. Three seconds after each stimulus, subjects were prompted by an auditory cue to verbally rate the perceived pain intensity on a numerical rating scale ranging from 0 (no pain) to 100 (maximum tolerable pain). Stimulation site was alternated block by block between the later control and the later placebo sites. The paradigm, thus, yielded 2 conditions, ie, a low-intensity and a high-intensity condition.

The second paradigm investigated top-down-mediated modulations of pain due to a placebo analgesia procedure (**Fig. 1C**). Placebo analgesia was preferred over alternative, eg, attention-/distraction-based methods of top-down modulation, as it represents a clinically highly relevant modulation of pain without confounds by other cognitive operations or stimuli from other modalities. To this end, 2 identical inert creams were applied to the subjects' hand in the waiting time between the first and the second paradigm. Participants were informed that they received an analgesic cream on the skin areas outlined in green and an inert control cream on the skin areas outlined in black. The creams were kept in professionally labeled tubes. After application, the creams were left on the skin for 15 minutes. Participants were told that the analgesic cream would take effect during this time. To enhance participants' expectations about an effective pain relief, Von Frey filaments of 2 different intensities (placebo site: 16 mN; control site: 128 mN) were applied to the hand after having wiped off the creams. Participants perceived the stimulation with closed eyes and were asked whether they perceived a difference in stimulation intensity between the placebo and control sites, which all of them did. The paradigm itself consisted of a conditioning and a test phase. In the conditioning phase, 20 low-intensity stimuli were applied to the

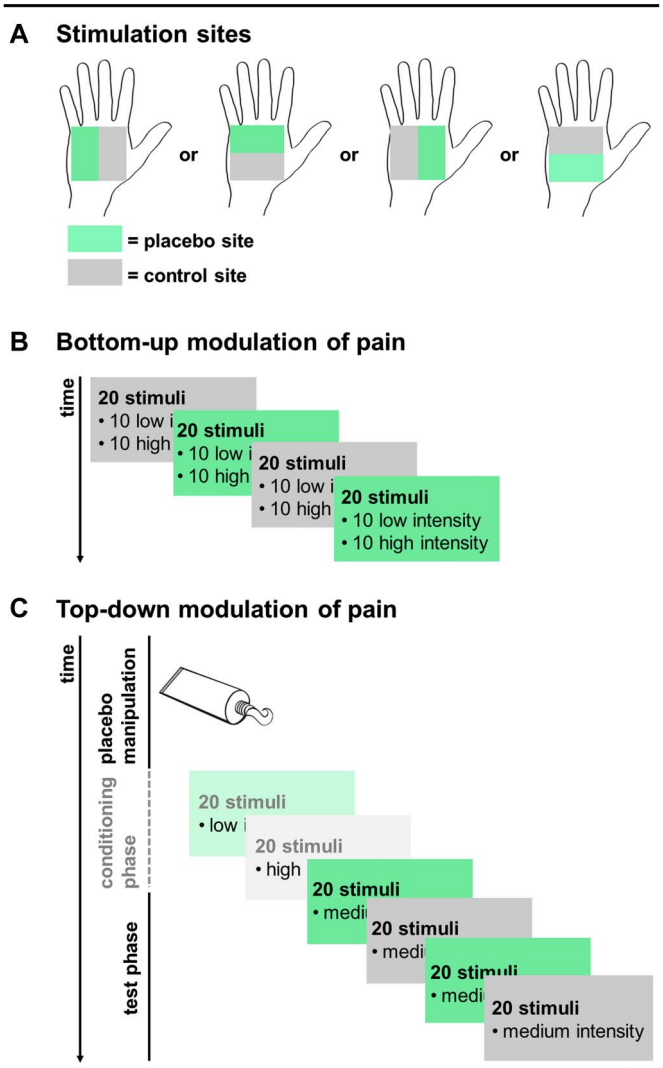

Figure 1. Procedure. (A) Stimulation sites for the 2 paradigms. The designation of the placebo and control sites had 4 different possibilities, which were counterbalanced across subjects. (B) The first paradigm investigated bottom-up modulations of pain administering painful stimuli with varying intensity. Forty low-intensity and 40 high-intensity stimuli were applied in pseudorandomized sequence in 4 blocks of 20 stimuli each, alternating between the 2 stimulation sites of the hand. (C) The second paradigm investigated top-down modulations of pain implemented by a placebo analgesia procedure. Two phases of painful stimulation followed the application of an allegedly analgesic cream to a part of the hand (the placebo site). In the conditioning phase, 20 low-intensity painful stimuli were applied to the placebo site and 20 high-intensity painful stimuli were applied to the control site. In the test phase, 80 medium-intensity stimuli were applied in blocks of 20 stimuli each, alternating between the placebo and the control sites. The analysis focused on the test phase exclusively.

placebo site of the hand and 20 high-intensity stimuli were applied to the control site of the hand. Unbeknown to the subjects, the test phase followed without interruption. Here, 80 medium-intensity stimuli were applied in blocks of 20 stimuli each, alternating between the placebo and the control sites of the hand. Three seconds after each stimulus, subjects were prompted by an auditory cue to verbally rate the perceived pain intensity. To reinforce the expectations about the efficacy of the analgesic cream, Von Frey filaments of 2 different intensities (placebo site: 16 mN; control site: 128 mN) were again applied to the hand after each stimulation block, and participants were asked again whether they experienced the pressure differently on the placebo and the control sites, which they did without exception. The test phase of the paradigm, thus, yielded 2 conditions, ie, a control and a placebo condition, with identical medium-intensity stimulation in both conditions.

For the duration of the entire procedure, participants were exposed to white noise through headphones to cancel out noise of the laser device. The participants perceived the stimuli with closed eyes.

2.4. Identification of placebo responders

To identify placebo responders, we determined the percentage difference in pain ratings for the placebo and control sites of the hand (paradigm 2) and subtracted the percentage difference in pain ratings for the correspondent sites of the hand before application of the cream (paradigm 1):

$$\text{placebo response} = \left(100 \times \frac{\text{rating}_{\text{paradigm2}_{\textit{placebo site}}}}{\text{rating}_{\text{paradigm2}_{\textit{control site}}}}\right) - \left(100 \times \frac{\text{rating}_{\text{paradigm1}_{\textit{placebo site}}}}{\text{rating}_{\text{paradigm1}_{\textit{control site}}}}\right).$$

In this way, we controlled for potential differences in sensitivity of the 2 stimulation sites. A participant was defined as a placebo responder if the placebo-induced decrease in pain ratings after correction for site differences in sensitivity was at least 20%.

2.5. EEG recordings and preprocessing

EEG data were recorded with an electrode cap (EasyCap, Herrsching, Germany) and BrainAmp MR plus amplifiers (Brain Products, Munich, Germany) using the BrainVision Recorder software (Brain Products). The input impedance of the amplifiers was 10 MΩ. The electrode montage included 64 scalp electrodes consisting of the electrodes Fz/Cz/Pz, FP1/2, F3/4/7/8, C3/4, P3/4, T3/4/5/6, and O1/2 of the 10-20 system and the additional electrodes FPz, AFz, FCz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, P1/2/5/6, TP7/8/9/10, and PO3/4/7/8/9/10. Two additional electrodes were fixed below the outer canthi of the eyes. During the recording, the EEG was referenced to the FCz electrode, grounded at AFz, sampled at 1000 Hz, and high-pass filtered at 0.015 Hz. The impedance of all electrodes was kept below 20 kΩ.

EEG data were preprocessed using the BrainVision Analyzer software (Brain Products). Offline analysis included downsampling to 512 Hz, digital high-pass filtering at 0.5 Hz, and re-referencing to the average reference. A regression approach from the BioSig software library[39] was used to remove 50 Hz line noise. Independent component analysis was used to correct for vertical and horizontal eye movements as well as muscle artifacts. Data were then segmented into trials from −1100 to 1500 milliseconds with respect to each laser stimulus. Trials with signal amplitudes exceeding ±100 μV in any channel were automatically rejected. The number of remaining trials after artifact correction was 32 (80%; range, 26-38) for the low-intensity condition, 30 (75%; range, 24-39) for the high-intensity condition, 33 (83%; range, 26-39) for the control condition, and 34 (85%; range, 26-38) for the placebo condition.

2.6. EEG data analysis

EEG data were analyzed using FieldTrip (Nijmegen, the Netherlands), an open-source toolbox for Matlab.[33]

2.6.1. Time-domain analysis of pain-evoked potentials

To assess the effects of bottom-up and top-down modulations of pain on laser-evoked potentials, the segmented data were low-pass filtered at 30 Hz and baseline corrected (baseline interval, −400 to 0 milliseconds). Single-trial waveforms were then averaged across trials for the low-intensity and high-intensity conditions and placebo and control conditions. For the statistical analysis, individual peak amplitudes were identified for the N1, N2, and P2 responses and compared between conditions. Electrodes (subsets) for comparison were electrode C4 for analysis of the N1 response and pooled electrodes Cz, FCz, and C2 for analysis of the N2/P2 response, respectively. For the analysis of the N1 response, data were re-referenced to Fz before averaging.[18]

2.6.2. Time–frequency analysis of pain-induced responses

To transform the data from the time to the time–frequency domain, a wavelet-based fast Fourier transformation was used. The length of the sliding window was 250 milliseconds, and it was moved in steps of 1 data point (1/512 seconds). After applying a Hanning taper, the power estimates were computed for a frequency range from 1 to 100 Hz and a time window from −1100 milliseconds to 1500 milliseconds with respect to painful stimulation. Baseline correction was performed by subtracting the power in the prestimulus interval from −800 to −200 milliseconds. Single-trial time–frequency data were then averaged across trials for each of the 4 conditions. Statistical analysis focused on 3 time–frequency regions of interest (ROIs) in the theta (4-8 Hz, 150-350 milliseconds), alpha (8-13 Hz, 500-1000 milliseconds), and gamma frequency range (70-90 Hz, 150-350 milliseconds), which have previously been shown to relate to changes in stimulus intensity and pain perception.[36] Theta and gamma responses were analyzed at pooled electrodes FCz, Cz, and C2, and alpha responses were analyzed at pooled electrodes FCz, Cz, CPz, C1, C2, CP1, CP2, FC1, and FC2. For each ROI, power was averaged across time, frequency, and electrodes.

2.7. Statistical analysis

Statistical analyses were performed using SPSS for Windows (IBM SPSS Statistics 21; IBM, Armonk, NY). Normal distribution of the data was confirmed for all variables by using the Kolmogorov-Smirnov test. Mean stimulus and pain intensities, peak amplitudes of pain-evoked potentials, and power values in defined ROIs from the time–frequency analysis were compared between conditions using 2-sided *t* tests for paired samples. To compare the effects of bottom-up- and top-down-mediated modulations on behavioral and

neuronal outcome measures, difference values of these measures were calculated between the 2 conditions of each paradigm. These difference values were then again compared using 2-sided *t* tests for paired samples. Please note that an analysis of variance could not be applied to the data, as the study did not comprise a full factorial 2 × 2 design. Level of significance for hypothesis testing was $P < 0.05$.

3. Results

3.1. Behavioral results

In the first paradigm, mean stimulus intensity was higher in the high-intensity condition (mean ± SD, 570 ± 68 mJ; range, 400-650 mJ) than in the low-intensity condition (480 ± 78 mJ; range, 300-610 mJ; $t = 11.8$; $P < 0.001$). In the second paradigm, the same (medium) stimulus intensities were used in the control and in the placebo conditions (540 ± 67 mJ; range, 390-630 mJ) (**Fig. 2A**).

Mean pain intensity ratings were higher in the high-intensity condition (51 ± 18) than in the low-intensity condition (38 ± 16; $t = 9.78$; $P < 0.001$). Likewise, pain intensity ratings were higher in the control condition (40 ± 19) than in the placebo condition (28 ± 19; $t = 7.31$; $P < 0.001$). Difference values of pain intensity in the high- vs low-intensity condition of the first paradigm and in the control vs placebo condition of the second paradigm did not differ significantly ($t = 0.54$, $P = 0.6$) (**Fig. 2B**). Importantly, before application of the cream, the pain ratings between the placebo and control stimulation sites of the hand did not differ significantly ($t = -1.93$, $P = 0.07$).

3.2. Influence of stimulus intensity and placebo analgesia on pain-evoked potentials

Average N1 and N2/P2 waveforms and topographies are depicted in **Figure 3**. To investigate the influence of stimulus intensity and placebo analgesia on N1 and N2/P2 responses, we compared peak amplitudes between conditions. Peak N1 amplitudes were higher in the high-intensity than in the low-intensity condition ($t = 2.34$, $P = 0.03$) and in the control than in the placebo condition ($t = 3.88$, $P = 0.001$). Difference values of amplitudes in the high- vs low-intensity condition and in the control vs placebo condition did not differ significantly ($t = -0.58$, $P = 0.57$), indicating that stimulus intensity and placebo analgesia similarly influenced N1 amplitudes.

Peak N2 amplitudes were higher in the high-intensity than in the low-intensity condition ($t = 3.09$, $P = 0.006$) and in the control than in the placebo condition ($t = 2.33$, $P = 0.031$). Difference values of N2 peak amplitudes in the high- vs low-intensity condition and in the control vs placebo condition did not differ significantly ($t = -1.51$, $P = 0.149$), indicating that stimulus intensity and placebo analgesia influenced N2 amplitudes in a similar way.

Peak P2 amplitudes between the high- and low-intensity conditions and between the control and placebo conditions did not differ significantly ($t = -1.36$, $P = 0.19$; $t = -1.6$, $P = 0.119$). Also, difference values of P2 amplitudes in the high- vs low-intensity condition and in the control vs placebo condition did not differ significantly ($t = -0.34$, $P = 0.741$).

Taken together, the N1 and N2 responses but not the P2 response were significantly and comparably modulated by both stimulus intensity and placebo analgesia.

3.3. Influence of stimulus intensity and placebo analgesia on pain-induced responses

Time–frequency analysis confirmed that painful stimulation yielded neuronal responses in the predefined ROIs (**Fig. 4**). In comparison to a prestimulus baseline, we found a significant increase of neuronal activity in the theta frequency range ($t_{min} = 4.55$, $P_{max} < 0.001$), reflecting pain-evoked potentials, a significant pain-induced decrease of neuronal activity in the alpha frequency range ($t_{min} = -3.22$, $P_{max} = 0.005$), and a significant increase of pain-induced neuronal activity in the gamma frequency range ($t_{min} = 2.38$, $P_{max} = 0.028$). To investigate the influence of bottom-up and top-down modulations on pain-induced neuronal responses, we compared neuronal activity in the 3 ROIs between conditions (**Fig. 5**).

Theta responses were significantly stronger in the high- than in the low-intensity condition ($t = 3.29$, $P = 0.004$) and in the control than in the placebo condition ($t = 3.6$, $P = 0.002$). Difference values of neuronal activity in the high- vs low-intensity condition and in the control vs placebo condition did not differ significantly ($t = 1.53$, $P = 0.143$).

Alpha responses were significantly stronger in the high- than in the low-intensity condition ($t = 13.57$, $P < 0.001$), but did not differ significantly between the control and placebo conditions ($t = 1.26$,

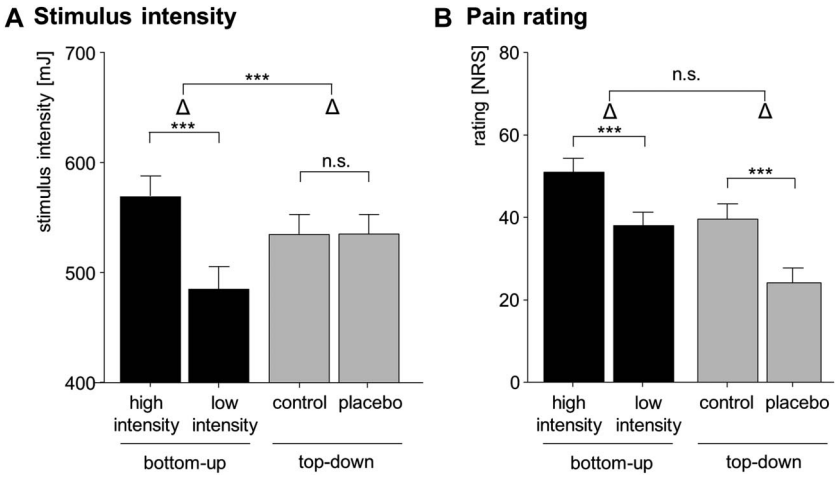

Figure 2. Behavioral data. (A) Mean (±SEM) stimulus intensities and (B) mean (±SEM) pain ratings (NRS, 0-100) for the 2 paradigms with 2 conditions each (high intensity/low intensity; control/placebo). ***$P < 0.001$. n.s., not significant. NRS, numerical rating scale.

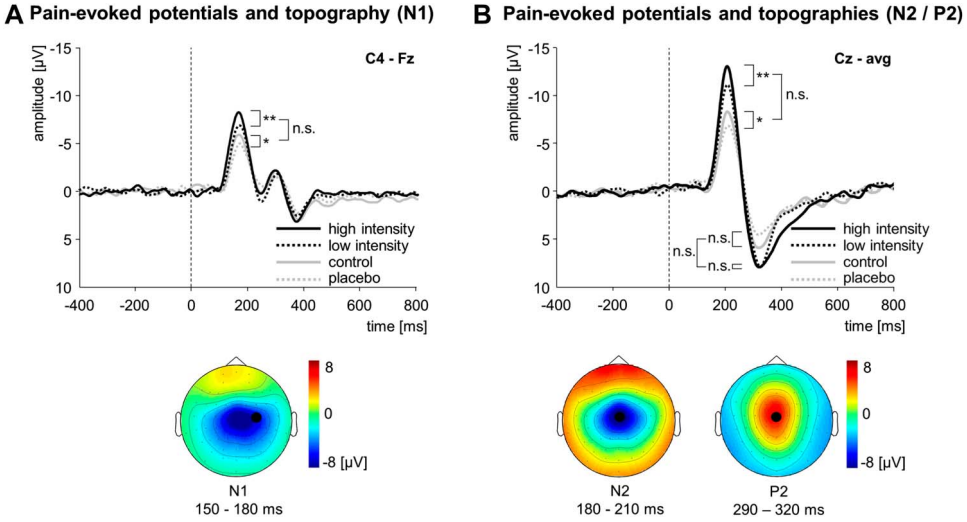

Figure 3. Pain-evoked potentials. (A) The upper panel shows the grand average time course of the N1 response in the 2 paradigms with 2 conditions each (high intensity/low intensity; control/placebo), displayed at the contralateral central electrode C4 (referenced to Fz). The lower panel shows the scalp distribution of neuronal activity between 150 and 180 milliseconds after painful stimulation averaged across all subjects and conditions. (B) The upper panel shows the grand average time course of the N2/P2 response in the 2 paradigms with 2 conditions each (high intensity/low intensity; control/placebo), displayed at the vertex electrode Cz (referenced to the average). The lower panel shows the scalp distributions of neuronal activity between 180 and 210 milliseconds (N2) and 290 and 320 milliseconds (P2) after painful stimulation averaged across all subjects and conditions. *$P \leq 0.05$; **$P \leq 0.01$. n.s., not significant.

$P = 0.225$). Consequently, difference values of alpha responses in the high- vs low-intensity condition and in the control vs placebo condition differed significantly ($t = 5.6$, $P < 0.001$).

Gamma responses were significantly stronger in the high- than in the low-intensity condition ($t = 2.74$, $P = 0.013$), but did not differ significantly between the control and placebo conditions ($t = 0.74$, $P = 0.467$). The comparison of the difference values of neuronal activity in the high- vs low-intensity condition and in the control vs placebo condition yielded a trend towards significance ($t = 2.02$, $P = 0.058$). Taken together, in line with the pain-evoked potentials, theta responses were significantly influenced by both stimulus intensity and placebo analgesia. In contrast, pain-induced alpha and gamma responses were significantly influenced by stimulus intensity but not by placebo analgesia.

4. Discussion

In this study, we investigated the neurophysiological coding of bottom-up and top-down modulations of pain implemented by changes in stimulus intensity and placebo analgesia, respectively. Our results show that pain-evoked potentials are similarly influenced by both stimulus intensity and placebo analgesia. In

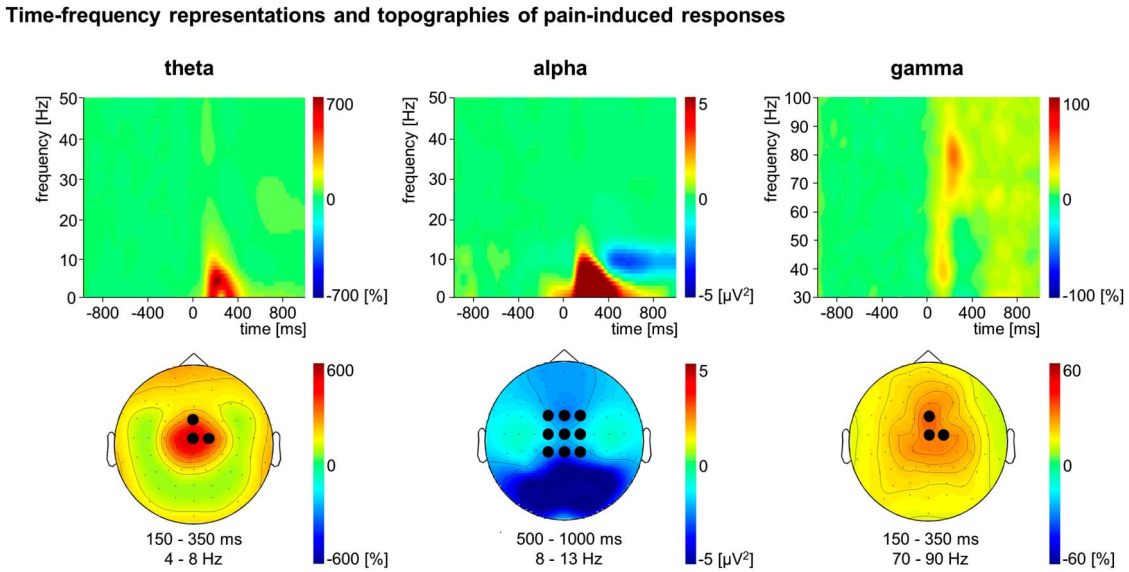

Figure 4. Pain-induced neuronal responses. The upper row shows time–frequency representations of neuronal activity in response to painful stimulation as compared to a prestimulus baseline (−800 to 200 milliseconds) averaged across all subjects and conditions. Responses were averaged across central electrodes as marked in the corresponding topographical maps of theta, alpha, and gamma responses in the lower row. For visualization only, TFRs and topographies illustrating gamma and theta responses are displayed as % signal change relative to baseline, whereas those illustrating alpha responses are displayed in absolute power minus baseline power. TFR, time–frequency representation.

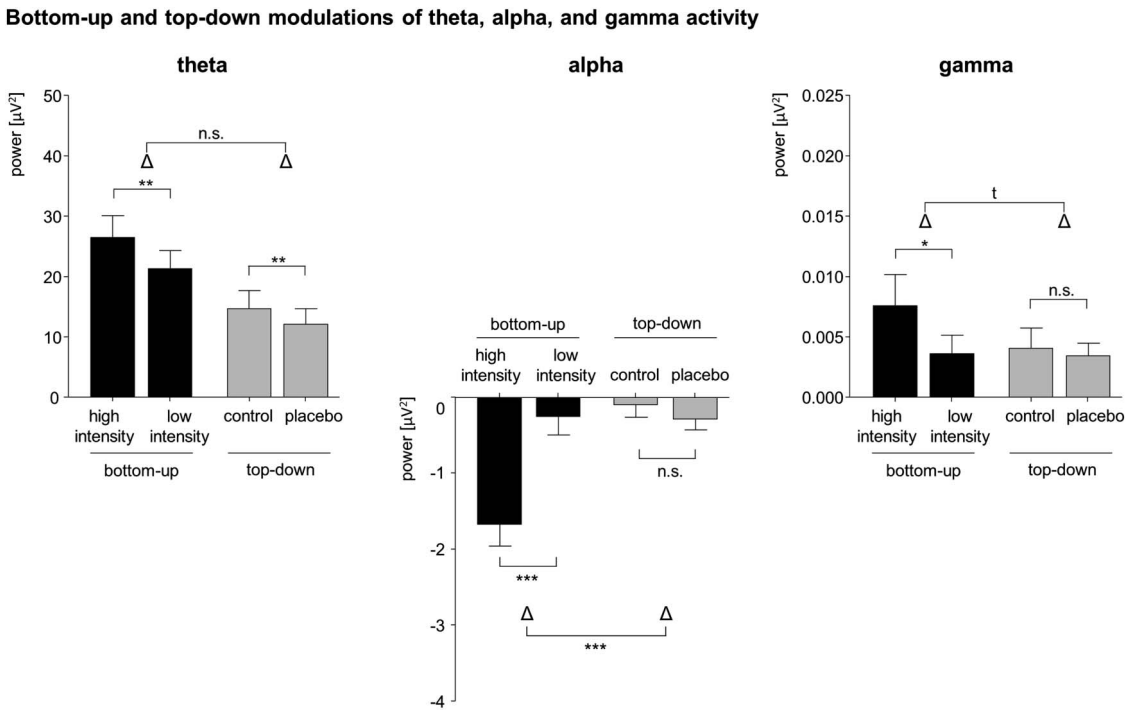

Figure 5. Comparison of bottom-up and top-down modulations of pain-induced responses. The panels show the mean power (±SEM) of theta, alpha, and gamma responses in the 2 paradigms with 2 conditions each (high intensity/low intensity; control/placebo). Statistical tests were based on absolute power minus baseline power for all frequency bands. *$P \leq 0.05$; **$P \leq 0.01$. n.s., not significant.

contrast, pain-induced alpha and gamma responses are sensitive to changes in stimulus intensity but not to the placebo manipulation. These findings indicate that pain-related neuronal responses can be differentially influenced by bottom-up- and top-down-mediated modulations of pain. They further reveal that the close relationship between gamma responses and pain perception shown in previous studies does not generalize to all modulations of pain.

With respect to pain-evoked potentials, we found that N1 and N2 responses are influenced by both stimulus intensity and placebo analgesia. An association between changes in stimulus intensity and amplitudes of N1[21] and N2[14,21,22] responses is in good accordance with previous findings. Similarly, previous EEG studies observed placebo effects on N2 responses.[3,9,27,29,42] To date, only a single study has investigated placebo effects on the N1 response[9] and did not find a significant effect. This outcome might be due to a different electrode selection for the investigation of the N1 response, which has been optimized according to recent suggestions in this study.[18] For the P2 response, we did not find a significant effect of stimulus intensity or placebo analgesia. Although there is recent evidence that the N2 response is more closely related to pain perception than the P2 response,[24] the majority of studies showed that the P2 response is also influenced by stimulus intensity[4,22,32] and placebo analgesia.[3,9,27,29,41,42] The lack of an effect in our study may be due to the fact that placebo effects on the P2 response can decrease over time[41] and that we applied 2 paradigms with a large number of stimuli. Taken together, our results indicate that pain-evoked potentials can be similarly influenced by different modulations of pain. Moreover, the lack of specificity complements recent evidence that pain-evoked potentials, which mostly originate from operculoinsular and cingulate cortices,[12] do not directly reflect stimulus intensity and/or pain intensity but rather the salience of painful events.[25]

Concerning pain-induced gamma responses, our results show a significant influence of stimulus intensity but not of placebo analgesia. This finding is in accordance with previous studies, which have shown that amplitudes of pain-induced gamma responses covary with stimulus intensity and pain intensity.[15–17,35,36,43] Anatomically, pain-induced gamma responses originate from somatosensory cortices.[15–17,37,43] Functionally, gamma oscillations have been suggested to reflect the local encoding of sensory, motor, or cognitive information.[10] Pain-induced gamma oscillations are therefore likely to reflect the sensory processing of nociceptive information at the level of the somatosensory cortex. Interestingly, previous studies have shown that under certain conditions, gamma responses can encode pain perception more reliably than other pain-related responses.[15,16,43] This close relationship between pain-induced gamma responses and pain perception was observed during explicit modulations[16] or spontaneous fluctuations[15,23] of attention to pain, which is known to affect early sensory processing stages of pain.[7] The present results reveal that this close relationship between gamma oscillations and pain perception does not generalize to placebo analgesia. This observation is well compatible with the notion that placebo analgesia influences higher-level affective, evaluative, and salience-related processes rather than sensory and/or attentional processing.[5–7] This compatibility is supported by functional imaging studies, which indicated that placebo manipulations affect pain processing in sensory cortices less consistently than in higher-level cortical areas related to salience and appraisal.[1,40] Taken together, our findings indicate that the relationship between pain-induced gamma oscillations and pain perception depends on the behavioral context. Gamma oscillations may be closely related to pain perception under circumstances where it is mostly influenced by sensory processing. In contrast, when affective, evaluative, and salience-related processes dominate, pain perception may be

more closely related to the less-specific pain-evoked potentials originating from operculoinsular and cingulate cortices than to gamma oscillations originating from primary somatosensory cortex.

We further observed that pain-related alpha decreases are significantly enhanced by higher stimulus intensity but not altered by a placebo procedure. A single previous study related alpha activity to placebo analgesia,[20] showing a placebo-associated increase of alpha oscillations. However, this study is only indirectly related to the present results, as alpha activity was recorded during a resting state after placebo induction. Moreover, the fact that we did not observe placebo modulations of alpha responses does not preclude a fundamental role of neuronal alpha oscillations in other modes of top-down processing, eg, in the attentional control of pain.[19,28,31]

Some limitations have to be considered with respect to the interpretation of the present findings. First, we implemented top-down modulations of pain by a placebo analgesia procedure because it represents a clinically relevant modulation without confounds by stimuli from other modalities. Our findings do, however, not necessarily generalize to all types of top-down modulation. Second, only placebo responders were included in this study to maximize the behavioral and the neuronal effects of the top-down modulation. This factor has to be taken into account when comparing the present results with previous studies that included both placebo responders and nonresponders[3,9,27,42] or differentiated between the 2 groups.[41] Third, top-down modulations of pain were performed in a fixed order after the bottom-up modulations. This fixed order of paradigms was chosen to avoid carryover effects from the placebo manipulation to later conditions. On the other hand, a fixed order implies the risk of order effects. Indeed, pain intensity was overall higher in the first than in the second paradigm, which most likely represents a habituation effect. Our main findings do, however, not relate to general differences of response amplitudes between paradigms but to modulations within the 2 paradigms, which induced comparable changes in pain intensity. We are, thus, confident that the overall decrease in pain intensity does not explain the observed qualitative difference in the neurophysiological encoding of both modulations.

In summary, our results show that pain-evoked potentials and pain-induced alpha and gamma responses are differentially sensitive to bottom-up and top-down modulations of pain. Our findings therefore indicate that pain-evoked potentials and pain-induced responses represent different aspects in the integration of bottom-up-mediated sensory information and top-down-mediated contextual information into a subjective percept. Pain perception is, thus, finally determined by the pattern of neuronal responses at different frequencies rather than by each response in isolation. With respect to pain-induced gamma responses, our observations reveal that the previously described close relationship to pain perception does not generalize to all types of pain modulation. Pain-induced gamma oscillations do therefore not represent an invariable biomarker of pain perception but rather a marker of local sensory processing whose role for pain perception depends on the behavioral context.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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