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RESEARCH ARTICLE | *Sensory Processing*

Early gamma-oscillations as correlate of localized nociceptive processing in primary sensorimotor cortex

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Heid C, Mouraux A, Treede RD, Schuh-Hofer S, Rupp A, Baumgärtner U. Early gamma-oscillations as correlate of localized nociceptive processing in primary sensorimotor cortex. *J Neurophysiol* 123: 1711–1726, 2020. First published March 25, 2020; doi:10.1152/jn.00444.2019.—Recent studies put forward the idea that stimulus-evoked gamma-band oscillations (GBOs; 30–100 Hz) play a specific role in nociception. So far, evidence for the specificity of GBOs for nociception, their possible involvement in nociceptive sensory discriminatory abilities, and knowledge regarding their cortical sources is just starting to grow. To address these questions, we used electroencephalography (EEG) to record brain activity evoked by phasic nociceptive laser stimuli and tactile stimuli applied at different intensities to the right hand and foot of 12 healthy volunteers. The EEG was analyzed in the time domain to extract phase-locked event-related brain potentials (ERPs) and in three regions of interest in the time-frequency domain (delta/theta, 40-Hz gamma, 70-Hz gamma) to extract stimulus-evoked changes in the magnitude of non-phase-locked brain oscillations. Both nociceptive and tactile stimuli, matched with respect to subjective intensity, elicited phase locked ERPs of increasing amplitude with increasing stimulus intensity. In contrast, only nociceptive stimuli elicited a significant enhancement of GBOs (65–85 Hz, 150–230 ms after stimulus onset), whose magnitude encoded stimulus intensity, whereas tactile stimuli led to a GBO decrease. Following nociceptive hand stimulation, the topographical distribution of GBOs was maximal at contralateral electrode C3, whereas maximum activity following foot stimulation was recorded at the midline electrode Cz, compatible with generation of GBOs in the representations of the hand and foot of the primary sensorimotor cortex, respectively. The differential behavior of high-frequency GBOs and low-frequency 40-Hz GBOs is indicating different functional roles and regions in sensory processing.

NEW & NOTEWORTHY Gamma-band oscillations show hand-foot somatotopy compatible with generation in primary sensorimotor cortex and are present following nociceptive but not tactile stimulation of the hand and foot in humans.

EEG; gamma-band oscillation; nociception; pain; time-frequency analyses

INTRODUCTION

Brief nociceptive stimuli are known to yield evoked potentials, the generators of which have been identified using both noninvasive and invasive recordings in humans and include the primary and secondary somatosensory cortex, the insula, the cingulate, and the thalamus (Apkarian et al. 2005; Garcia-Larrea et al. 2003; Schnitzler and Ploner 2000). A large body of evidence from clinical studies has demonstrated that high-intensity infrared laser-evoked potentials (LEP) and contact heat-evoked potentials reflect activity related to the activation of nociceptive pathways (Treede et al. 2003; Valeriani et al. 2012). However, under some conditions, the correlation between subjective pain intensity and amplitude of these responses is disrupted in healthy volunteers (Treede et al. 2003; Zhang et al. 2012), and some brain regions that are activated by nociceptive stimuli thereby producing these responses are also activated by stimuli of other sensory modalities e.g., visual or auditory (Iannetti and Mouraux 2010; Mouraux et al. 2011; Mouraux and Iannetti 2009; Treede et al. 1988).

On the other hand, nociceptive stimuli also evoked changes in the magnitude of oscillatory brain activity that is not phase locked and recently has been discussed as potential candidate for a biomarker of nociception or pain. This evoked activity was found as a brief increase in gamma power in the 40- to 100-Hz frequency range, whose magnitude appears to correlate better with subjective pain intensity than the amplitude of phase-locked evoked potentials and could thus be a more specific marker for nociception (Gross et al. 2007; Zhang et al. 2012). Besides gamma-band oscillations (GBOs), nociceptive stimuli also induce changes in the magnitude of oscillations in other frequency bands, such as a suppression of alpha-band (7–13 Hz) and beta-band oscillations (13–30 Hz), a respective rebound of beta-band oscillations, and an increase in power of low-frequency delta oscillations (0–5 Hz) (Hauck et al. 2007; Mouraux et al. 2003; Nickel et al. 2017; Ohara et al. 2004a; Raij et al. 2004).

GBOs are not only elicited by nociceptive stimuli. Instead, they can be elicited by a large array of sensory stimuli and cognitive tasks. They can be observed both during waking and sleep (Buzsáki and Wang 2012) and can be modulated by slower rhythms through cross-frequency coupling (Buzsáki and Wang 2012), e.g., cross-frequency coupling between the

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amplitude of GBOs and the phase of theta oscillations (Mormann et al. 2005; Wang 2002) or alpha oscillations (Cohen et al. 2009). GBOs per se should thus not be considered as a feature specific for nociceptive processing. Nevertheless, GBOs elicited by nociceptive stimuli might reflect cortical activity specifically related to the processing of nociceptive input. So far, evidence suggesting that nociception-evoked GBOs could constitute a marker of nociceptive-specific cortical activity was the finding, that GBO power remains more or less constant together with the perception of pain intensity, when phasic nociceptive stimuli of the same intensity are applied at a rate of 1 Hz, whereas the magnitude of phase-locked evoked potentials strongly habituates (Zhang et al. 2012). Interestingly, following hand stimulation, nociception-evoked GBOs recorded using surface EEG and magnetoencephalography were shown to be maximal over the contralateral hemisphere, leading authors to suggest that the activity may originate predominantly from the contralateral primary somatosensory cortex (S1) (Gross et al. 2007; Zhang et al. 2012) and/or the primary motor cortex. However, lateralized responses could also be expected if, for example, the stimulus-evoked GBOs originated from the contralateral secondary somatosensory cortex and/or the insula.

The present study followed two objectives. The first objective was to further explore the specificity of nociception-evoked GBOs by examining whether these are observed only following nociceptive stimulation, or whether they can also be elicited by nonnociceptive tactile stimuli (Baumgärtner and Treede 2009). The second objective was to examine whether nociceptive stimuli delivered to the hand and foot would elicit GBOs having scalp topographies compatible with S1 somatotopy, i.e., examine whether GBOs elicited by stimulation of the hand are maximal over contralateral central electrodes, whereas GBOs elicited by stimulation of the foot are maximal over the vertex, as would be expected considering the lateral and medial representations of the hand and foot in S1. The related three hypotheses were that *1*) GBOs are elicited by nociceptive but not tactile stimuli, that *2*) the surface topography changes following nociceptive hand (lateralized toward contralateral central electrodes) or foot stimulation (central vertex distribution), and that *3*) GBOs increase with stimulus intensity.

For this purpose, we recorded the EEG responses to nociceptive laser stimuli and nonnociceptive tactile stimuli to the hand and foot of 12 healthy volunteers, matched for perceived intensity. We found that only nociceptive stimuli induced a significant enhancement of GBOs, whose magnitude increased with increasing stimulation intensity and pain perception, compatible with intensity coding. Moreover, the topographical distribution of nociception-evoked GBOs were maximal over left central electrodes when stimulating the right hand, and maximal over the scalp vertex when stimulating the right foot, compatible with activity originating predominantly from S1.

MATERIAL AND METHODS

Participants. Twelve healthy participants (6 women and 6 men) with an average age of 25 yr (range 22–28 yr) participated in the study. The study was previously approved by the ethics committee of the Medical Faculty Mannheim at Heidelberg University, and the details of the experiment were explained according to the Declaration of Helsinki, including the possibility to quit the experiment at any time. Each volunteer signed an informed consent and was later paid for participation. After the subjects agreed to participate in the study, we conducted a brief measurement of skin sensitivity at the dorsum of the right hand and foot. This preliminary check was done to document that no subject had a reduction of tactile or nociceptive perception at either of the two stimulation sites. The sensitivity test was semiquantitative and included an assessment of vibration sense using a 128-Hz tuning form, position sense by passive finger and toe movements, tactile sensitivity by touching the skin with cotton wool and with calibrated von Frey hairs, nociception by pinpricks, and thermoception by warm and cold water-filled test tubes (Spiegel et al. 2000, 2003). According to this test, all subjects had normal skin sensitivity in the areas to be tested. Subsequently, pain thresholds were determined to assess the individual pain sensitivity of each participant to determine the three laser intensities (energies) to be applied in the experiment. Before and after the experimental procedure, the skin temperature in the area where the stimuli were applied was measured using an infrared thermometer.

Nociceptive stimuli. Painful laser stimuli were generated by a Thulium-YAG laser (Themis, StarMedTec Starnberg, Germany) with a wavelength of 2.01 μm, a beam diameter of 5 mm, and a pulse duration of 1 ms. It was shown in previous studies that such laser stimuli activate selectively A-delta and C fiber nociceptors in the most superficial skin layers and are therefore an adequate stimulus to elicit nociceptive responses (Bromm and Treede 1987; Iannetti et al. 2006; Mouraux et al. 2010; Plaghki and Mouraux 2003; Treede et al. 2003). The hand piece was equipped with a visible laser, to indicate the area where the infrared laser beam was transmitted.

Tactile stimuli. The tactile stimuli were applied using a self-built pneumatic stimulator, which was connected to the compressed air system of the clinic. Inside the stimulator, two computer-controlled valves could release air pressure pulses of two different intensities which were delivered to the subject through plastic tubes. At the end of the tubes, a clip with a small plastic membrane (area 0.5 cm^2) conveyed, when the valves opened, short pressure pulses of 60-ms duration with adjustable intensity. The clips were attached to the hand and food dorsum with a soft bandage. The stimulator was controlled by a laptop that also sent out TTL pulses to the EEG trigger input, adjusted for the conduction time (delay) of the pneumatic stimulus (for details see Özcan et al. 2005).

Paradigm. To answer the questions of intensity coding, specificity, and somatotopy, nociceptive laser stimuli and tactile pneumatic stimuli of different intensities were applied under conditions as similar as possible to the hand and foot (Fig. 1, *A* and *C*). Each single block consisted of either 90 laser stimuli or 90 pneumatic stimuli. Laser stimuli were applied in a pseudo-randomized order with three intensities (30 stimuli each per block): *1*) individual pain threshold, *2*) intermediate intensity, *3*) fixed maximum intensity (hand: 540 mJ, foot: 600 mJ; Spiegel et al. 2000). Due to the hardware restrictions (two separate valves), only two intensities could be applied using the pneumatic stimulator. The chosen intensities were two and four bars (45 stimuli each per block) for every subject (Hoechstetter et al. 2000; Özcan et al. 2005), also applied in pseudo-randomized order. The interstimulus interval for both modalities was varied between 6.0, 6.5, and 7.0 s to avoid habituation. The order of blocks was balanced across subjects, with mirrored order within subjects. Individual intensity ratings were acquired by means of verbal ratings on a 0–100 numerical scale. For pain ratings, 100 was defined as the most intense pain the person could imagine and 0 was defined as no pain. For tactile ratings, 100 was defined as the strongest feeling of pressure on the skin that could be imagined, without being painful, and 0 was defined as no feeling of touch or pressure at all.

EEG recording. We attached 17 electrodes to the scalp, according to the international 10-20 system mounted in an electrode cap (FMS, Easy Cap Germany; Fig. 1*B*). The reference electrode was attached to the right earlobe (ipsilateral to stimulation). Before the experiments, electrode impedances were checked to be below 5 kΩ. The sampling

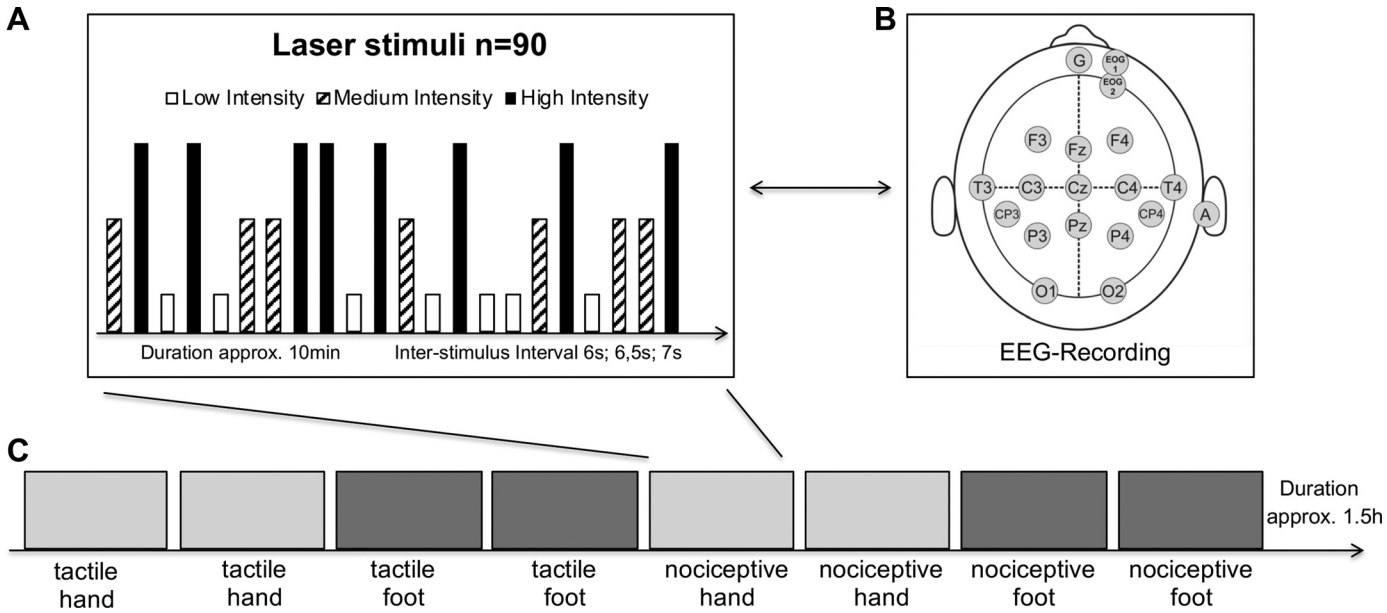

Fig. 1. Experimental paradigm, example for one subject, with one block (condition laser stimulation) extracted and shown in detail (*A*): Four different stimulus conditions (tactile hand, tactile foot, nociceptive hand, nociceptive foot) with one repetition in mirrored order were applied in 8 stimulation blocks to each subject (*C*). Between each block there was a short break of ~2–3 min. Both tactile and nociceptive stimulation blocks lasted approx. Ten minutes, contained 90 stimuli (tactile blocks: 2 different intensities; nociceptive blocks: 3 different intensities), and had varying interstimulus intervals of 6.0 s, 6.5 s, and 7.0 s. EEG-recording was done with standard EEG caps and contained 17 scalp electrodes (*B*).

rate of the EEG recording was 1 kHz. The subjects were seated in a comfortable chair in an electrically shielded room, where they had to sit calmly and as relaxed as possible. They were advised to look at a fixation point to avoid eye movements. Electrodes above and below the eyes (EOG1, EOG2) were used to control for blink artifacts.

EEG analysis and preprocessing. Analysis of the EEG data was carried out with Letswave 6, an open source MATLAB toolbox (A. Mouraux; https://www.letswave.org/). The first step of preprocessing was to apply a bandpass filter between 0.3 Hz and 100 Hz to the continuous EEG data. The second step was to segment the EEG data with respect to the different stimuli (laser hand, laser foot, tactile hand, tactile foot) and intensities, between 1 s prestimulus and 2 s poststimulus. A baseline correction was then applied using a −0.5 to 0 s prestimulus interval (Hu et al. 2014). An ICA (independent component analysis) was used to remove eye movement and eye blink artifacts (Delorme and Makeig 2004; Jung et al. 2001; Makeig et al. 1997). Each epoch was inspected for muscle artifacts by checking for the presence of high-frequency activities predominating at temporal and/or frontal electrodes. Finally, we split the data into two separate data sets, one data set low-pass filtered <30 Hz to identify low-frequency responses including the phase-locked ERP, the second data set high-pass filtered >30 Hz to identify high-frequency GBOs.

Time-frequency analysis. Time-frequency decomposition of the EEG epochs was achieved using a continuous Morlet wavelet transform (CWT) (Mouraux et al. 2003; Tiemann et al. 2010). The Morlet wavelet consists of a complex exponential localized in time by a Gaussian envelope. The spread of the Gaussian function was set to $0.15/\pi\omega_0$ when assessing the amplitude of low-frequency oscillations (<30 Hz) and $0.25/\pi\omega_0$ when assessing the high-frequency oscillations ($\omega 0$ corresponding to the central frequency of the wavelet). These different ratios were chosen to optimize the time-frequency resolution in the two frequency bands. For the low-frequency data set, explored frequencies ranged from 0.3 to 30 Hz. For the high-frequency data set, they ranged from 30 to 100 Hz. The modulus of the CWT was used as an estimate of amplitude. For construction of the time frequency maps a baseline correction was performed. During this procedure, for each time-frequency bin of each frequency line, the average amplitude of the last 500 ms of the prestimulus segment (−500 to 0 ms) was subtracted.

Region of interest analysis. To compare and analyze the final time-frequency maps with respect to differences between the intensity, the location, and the modality of stimuli (noxious versus tactile) we used a statistical comparison of corresponding region of interests (ROIs) (Gross et al. 2007; Zhang et al. 2012). In the final time-frequency maps we defined three regions of interest we wanted to compare statistically: first, the most important region of interest of this study containing the stimulus-induced GBO; second, a region of interest containing the stimulus evoked activity in the lower gamma 40-Hz band; and third, a region of interest containing the stimulus-evoked activity in the delta/theta band (Northon et al. 2019). The reason why we included a ROI at 40 Hz is, that this was one of the first reports of a gamma response induced by sensory, mainly auditory stimuli (Pantev 1995) and was considered to serve as a control. The position of the region of interest both in the delta/theta band and in the 40-Hz band was chosen to be the same for the four different conditions (noxious stimuli, tactile stimuli, hand stimulation, and foot stimulation). The position of these regions of interest was chosen in accordance with previous studies, identification of the maximum amplitude in the different frequency bands (Northon et al. 2019; Ploner et al. 2017) (Fig. 3; Table 1).

Since the amplitude of the stimulus-induced activity in the gamma-frequency band was proportionally less and more difficult to detect and to analyze, we chose to adjust that region of interest both for the differences in peripheral conduction distance between stimulation at the hand and foot and for the difference in conduction velocity between laser and pneumatic stimuli. To define the different positions of the regions of interest for each condition we used a multiple step approach. We first defined the ROI for laser-evoked GBOs elicited by hand stimulation based on a priori knowledge [results found in previous studies by Gross et al. (2007), Tiemann et al. (2010), and Zhang et al. (2012)] as extending between 0.150 and 0.230 ms (width 80 ms) after stimulation onset (coinciding with the LEP N1 and N2 latencies), and between 65 and 85 Hz (Gross et al. 2007; Tiemann et al. 2010; Zhang et al. 2012). As ROI for the putative GBOs following tactile hand stimulation, we used a time window of equal frequency

range and length and adjusted the location of this ROI according to the difference in latency of the N2 and P2 waves elicited by laser and tactile stimuli at the hand (Table 1). Second, we defined the ROIs for laser stimulation of the foot, and tactile stimulation of the foot, using the difference in latency of the (late) positive wave obtained in the different conditions as rough estimate of the effect of peripheral conduction time shifting the ROIs for laser foot stimulation by 48 ms and for tactile foot stimulation by 20 ms in time (compared with hand stimulation). The result were three different regions of interest for the four conditions (Table 1). Furthermore, we analyzed the amplitude changes of the phase-locked late evoked potentials (EPs; laser N2P2, tactile N1P1) in the poststimulus EEG for each condition and channel. Besides the late EPs we additionally analyzed the early P30/P50 wave in the poststimulus EEG for pneumatic stimuli. The P30 for pneumatic stimulation of the hand and the P50 for pneumatic stimulation of the foot are known as correlates of the primary cortical response of tactile input into the primary somatosensory cortex [correlate of the N20/P40 wave for clinical electrical median/tibial nerve stimulation (Allison et al. 1991)] showing a clear lateralization for stimuli applied to the hand and central distribution following stimulation of the foot and can therefore be used for quality control of the data (Hoechstetter et al. 2000, 2001).

Since the LEP N1 component is thought to be closer related to the sensory aspect of nociception and pain than the N2P2, albeit with lower signal-to-noise ratio, we looked whether rereferencing the data to Fz would yield additional information. As there is no a priori knowledge about specific GBO responses, we chose the same ROIs as indicated above (for the N-P vertex potentials) for the analysis, with the exception that the N1 ROIs for laser hand and foot stimulation were shifted in time 10 ms earlier (based on the hypothesis that the N1 response occurs earlier than the N2).

Statistics. Psychometric intensity ratings were analyzed using a two-factorial ANOVA for repeated measurements with the two factors stimulus location (hand versus foot) and intensity (laser: high–medium–low; tactile: low versus high). To analyze topographical differences, two-way ANOVAs were employed within each modality (nociceptive, tactile) for the highest stimulus intensity only, to look for lateralized or centralized brain responses following hand and foot stimulation based on the interaction of the factors stimulus location * electrode. As second step, a post hoc analysis was performed using paired-sample *t* tests with Bonferroni–Holm correction for multiple comparisons.

To validate the presence of a gamma response as such, a single-sided *t* test (for increases) was performed comparing each amplitude estimate of the baseline-corrected time-frequency matrices against zero (after prior baseline correction).

Intensity coding of brain responses within each of the two modalities (nociceptive, tactile) was tested using three-factorial ANOVAs for repeated measurements to investigate EP amplitudes, power within ROIs in the delta-theta, low (40 Hz), and high (70 Hz) gamma frequency range (factor intensity/energy) together with stimulus location (factor stimulus location; hand versus foot) and electrode location (factor electrode; C3, Cz, C4).

To analyze intermodality differences in GBO power between nociceptive and tactile stimuli, another two factorial ANOVA with the main factors of stimulus modality and stimulus location (hand/foot) was performed.

Generalized η^2 values were computed to report the effect sizes as revealed by the ANOVAs. For all ANOVAs with repeated measurements the *P* values of the *F*-tests were derived based on adjustments according to Greenhouse and Geisser. All statistical comparisons were carried out using aov_ez procedure of R (3.6.0).

Table 1. *Boundaries of regions of interest in the time and frequency space for the three different frequency bands [delta/theta, low gamma (40 Hz), and high gamma]*

N2 Latency	P2 Latency	Regions of Interest	*x*-Axis	*y*-Axis
		ROI: Delta/Theta	0–1.0 s	0.3–7 Hz
		ROI: 40 Hz	0–0.25 s	40–55 Hz
		ROI: GBO		
0.121 s	0.199 s	1. tactile hand	0.033–0.113 s	65–85 Hz
0.140 s	0.219 s	2. tactile foot	0.053–0.133 s	65–85 Hz
0.186 s	0.316 s	3. laser hand	0.150–0.230 s	65–85 Hz
0.199 s	0.364 s	4. laser foot	0.198–0.278 s	65–85 Hz

GBO, gamma-band oscillation; ROI, region of interest.

RESULTS

Ratings. The subjective ratings given by the participants after tactile stimuli increased significantly with the intensity of the tactile stimuli [intensity: $F(1,11) = 12.75$, $P = 0.004$, $\eta^2 = 0.008$], with no main effect for stimulus location [$F(1,11) = 2.50$, $P = 0.14$]. We did observe a marginal interaction between tactile stimulation intensity and stimulus location [$F(1,11) = 5.73$, $P = 0.04$, $\eta^2 = 0.0001$]. A comparable clear main effect of stimulation intensity was found for the painful laser stimuli [$F(1,11) = 15.86$, $P = 0.002$, $\eta^2 = 0.298$; Fig. 2*B*], without significant effect of stimulation site [stimulus location; $F(1,11) = 0.78$, not significant] nor interaction [$F(2,22) = 2.25$, $P = 0.13$). Both tactile stimuli of high and intermediate intensities and noxious stimuli of high and intermediate intensities were perceived as equally intense [tactile hand 22 ± 4 versus laser hand 20 ± 5 (containing only high and intermediate intensity); tactile foot 18 ± 4 versus laser foot 19 ± 5 (containing only high and intermediate intensity)].

Responses in the time domain and the time frequency domain: overview. Figure 3 illustrates both the responses at electrode C3 and at electrode Cz following nociceptive (laser) and tactile (pneumatic) stimuli of the highest intensity averaged across all subjects, when stimuli were applied to the right hand and foot. The late evoked potentials (EPs) depicted in the Fig. 3, *bottom* exhibited the typical biphasic N2P2 responses in the time domain. For tactile stimulation, an additional early downward deflection indicates the P30 as cortical response (N20 not visible). Figure 3, *middle* and *top* illustrate responses in the time-frequency domain for low (*middle*) and high-frequency activity (*top*) with different scaling (on average by a factor of 75), since the low-frequency (delta/theta) correlate of the evoked potential has by far more power than the responses at higher frequencies. The low-frequency response (delta/theta, Fig. 3, *middle*) coincided with the duration of the evoked potential as a whole, while the 40-Hz low-frequency gamma response and the 65–85 Hz high GBO (induced by nociceptive stimuli only), if present, were brief in activity coinciding with the early peak of the N2P2 EP response.

N1 analysis. Figure 4 illustrates both the responses at electrode C3 and at electrode Cz following nociceptive (laser) and tactile (pneumatic) for Fz rereferenced data for stimuli of the highest intensity averaged across all subjects, applied to the right hand and foot. As expected, amplitude and shape of the LEP [and somatosensory-evoked potential (SEP)] N1 were different from the LEP vertex response in the time domain (average latencies: laser hand: 164 ms, laser foot: 197 ms, tactile hand: 80 ms, tactile foot: 108 ms; compare Table 1, Fig. 3). The low-frequency response (delta/theta, Fig. 4, *middle*) coincided with the duration of the evoked potential as a

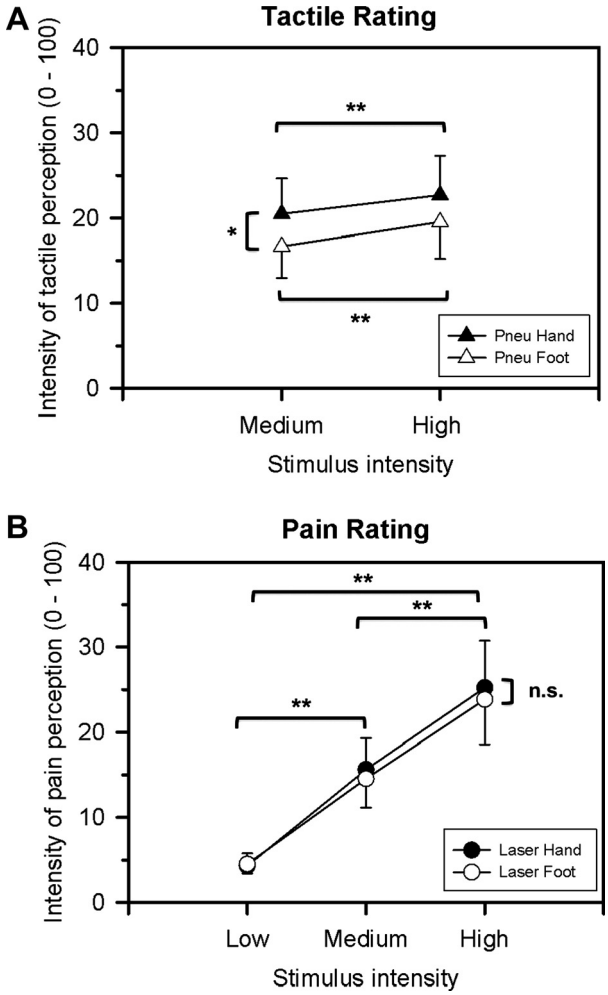

Fig. 2. Intensity ratings on a numerical rating scale (0–100) of all participants ($n = 12$) after tactile [pneumatic (Pneu)] stimuli (*A*), after painful (laser) stimuli (*B*). Data are presented as means ± SE. *$P < 0.05$; **$P < 0.01$; n.s., not significant; Student's paired-sample *t* tests, adjusted for multiple comparison by Bonferroni–Holm correction, when three values where compared (*B*).

whole, the 40-Hz gamma response (if present) might be interpreted as extension in the upper frequency range of the low-frequency response. The 65–85 Hz high GBO was induced by nociceptive stimuli only, and if present, was brief in activity coinciding with the early peak of the N1 EP response.

GBO significance test. To support our a priori defined ROIs for the analysis of the high (65–85 Hz) and low (40 Hz) gamma frequency, we performed a single-sided *t* test showing significant increases compared with "zero." As illustrated in Fig. 5, *middle*, a circumscribed significant increase is visible in the ROI for the high-frequency gamma response. Effect sizes for these results, comparing the prestimulus baseline (−0.5 to 0 s; at 65–85 Hz) with the data from our predefined ROIs, yielded a strong effect ($d' = 0.79$) for laser stimuli applied to the hand measured at C3, a comparable strong effect for Cz ($d' = 0.76$), and a small effect for channel C4 ($d' = 0.2$).

Somatotopy. All measures of amplitude or power exhibited a local maximum as indicated by a significant main effect of the factor *electrode*, except the gamma power following tactile stimuli (Table 1). Of less importance with respect to topography, the second main factor by itself, location (*stimulus location*; hand, foot), significantly influenced amplitude/power for the high-intensity nociceptive stimuli for the parameters "evoked potential" and the related "delta/theta" evoked activity. Finally, and most importantly, the interaction between the factors stimulus location and electrode was significant for the high-intensity nociceptive stimuli for the parameters "evoked potential," the related "delta/theta" evoked activity, and laser-induced high-frequency gamma power (GBO; Table 1). The later confirmed one of the main hypotheses, that nociceptive GBOs show somatotopic cortical/scalp organization.

The post hoc analysis yielded more detailed results: Following nociceptive stimulation, the EPs (positivity of the N2P2 late EP response) showed the maximum amplitude at the central vertex (Cz) electrode and statistically significant lower amplitudes at the contralateral and ipsilateral, central electrodes (Fig. 6, *A* and *B*). The same spatial pattern could be observed analyzing the ROI of the delta/theta-band in the low-frequency range (Fig. 6, *C* and *D*). In contrast, nociceptive GBOs had the highest intensity at the contralateral electrode (C3) for stimuli applied at the hand and at the central vertex electrode (Cz) for stimuli applied at the foot [Fig. 6, *E* and *F*, effect sizes: laser hand (C3 and Cz versus C4): $d' = 0.4$, laser foot (C3 and C4 versus Cz): $d' = 0.3$]. For the foot, post hoc comparisons between electrodes were not significant (lower signal-to-noise ratio).

For tactile stimuli, the EPs both for stimuli applied at the hand and foot showed the maximum amplitude at the central vertex (Cz) electrode and statistically significantly lower amplitudes at the contralateral and ipsilateral, central electrodes (Fig. 7, *A* and *B*) similar to the nociceptive responses. The same spatial pattern could be observed analyzing the ROI of the delta/theta-band in the low-frequency range (Fig. 7, *C* and *D*). Pneumatic stimuli led to decreases in the high gamma band without clear indication of topographic differences (Fig. 7, *E* and *F*).

Surface field distributions of nociceptive and tactile responses are shown in Fig. 8, *A* and *B*), which illustrates the statistical findings described above (Fig. 7) visually. The late EPs showed the comparable surface fields for both modalities and stimulus localizations (Fig. 8, *A* and *B*, *top*). A related pattern could be observed for the low-frequency (delta/theta) response (Fig. 8, *A* and *B*, *middle*). The GBO, which was only observed following laser stimuli, was lateralized following hand stimulation and vertex-centered following foot stimulation (Fig. 8*A*, *bottom*). To verify the quality of our tactile control data, we added the analysis of the P30-/P50-wave to our analysis, corresponding to the early median and tibial nerve SEP elicited by tactile (pneumatic) stimuli (Fig. 8*B*, *bottom*). Concerning somatotopy of tactile and nociceptive stimuli, both the high GBO after painful stimuli and the early P30/P50-wave after tactile stimuli had their maximum amplitude with lateralized voltage distribution after hand stimulation and vertex distribution after foot stimulation (Fig. 8, *A* and *B*, *bottom*; see also Table 1).

Intensity coding. We examined the relationship between stimulus intensity and amplitude or power changes in the prior defined ROIs of the evoked potential, response in the delta/theta-band (correlate of the EP in the time-frequency domain) and the ROI containing the high GBO at 65-85 Hz (Table 2, Fig. 9). The main effect of stimulation intensity in the ANOVA was significant for evoked potential amplitudes of both modalities (nociceptive, tactile; Table 2). The 40-Hz low-frequency gamma response did not code intensity as main effect (neither

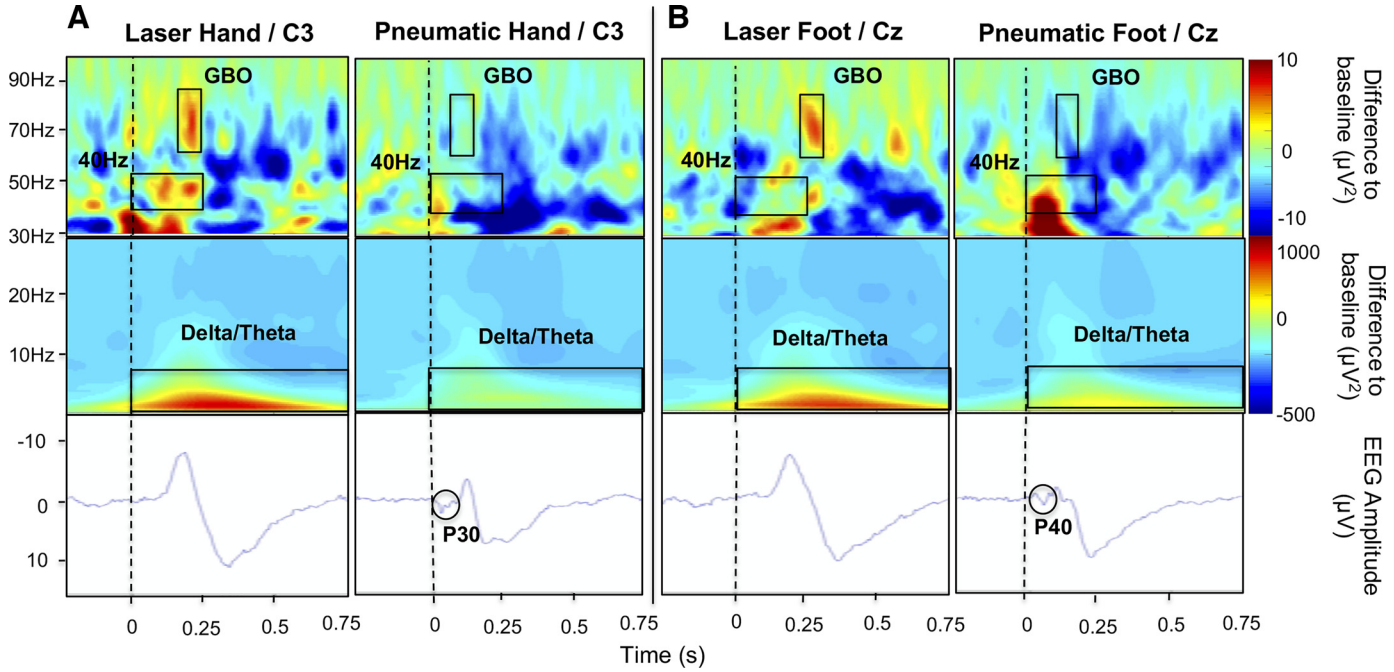

Fig. 3. Responses to high-intensity laser stimuli and pneumatic stimuli applied at the right hand (*A*) and high-intensity laser stimuli and pneumatic stimuli applied at the right foot (*B*) measured at electrodes C3 and Cz. Phase-locked responses (evoked potentials) are shown at the *bottom*, responses in the time-frequency domain are shown at *top*. Three different regions of interest in the time domain and the time-frequency domain were defined (before the statistical analysis), indicted by black frames. The identified responses were of different amplitude; note different scales (to the right).

nociceptive nor tactile), however the nociceptive evoked delta/theta power (related to the EP) as well as the high-frequency gamma response (GBO, $P=0.007$) did code intensity as main effect (Table 2).

Effects of intensity (energy) on the different measures of brain activity are summarized in Fig. 9 and Table 3. For hand stimulation, the amplitude of the late EP increased with stimulus intensity and was significantly larger for high compared to lower intensities for both nociceptive and tactile responses (high versus medium laser intensity, $P < 0.001$, t test, $d' = 1.09$; medium versus low laser intensity, $P < 0.01$, t test, $d' = 1.59$; high versus low laser intensity, $P < 0.001$, t test, $d' = 3.21$; high versus low tactile intensity, $P < 0.05$, t test, $d' = 0.5$; Fig. 9, *A* and *B*). Analysis of the relationship between the ROI contain-

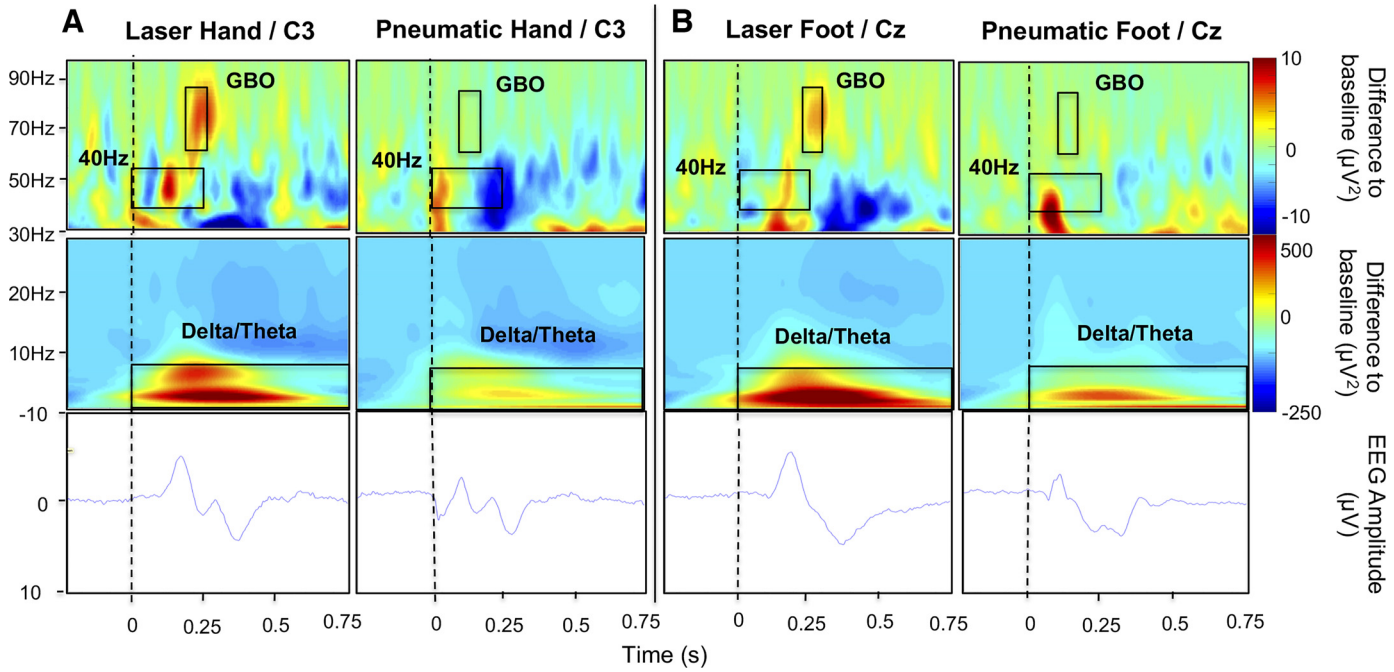

Fig. 4. N1 analysis (Fz reference). Responses to high-intensity laser stimuli and pneumatic stimuli applied to the right hand (*A*) and high-intensity laser stimuli and pneumatic stimuli applied at the right foot (*B*) measured at electrodes C3 and Cz. Phase-locked responses (evoked potentials) are shown at the *bottom*, responses in the time-frequency domain are shown at *top*. Three different regions of interest in the time-frequency domain are indicated by black frames (defined before the statistical analysis). Identified responses were of different amplitude; note different scales (to the right).

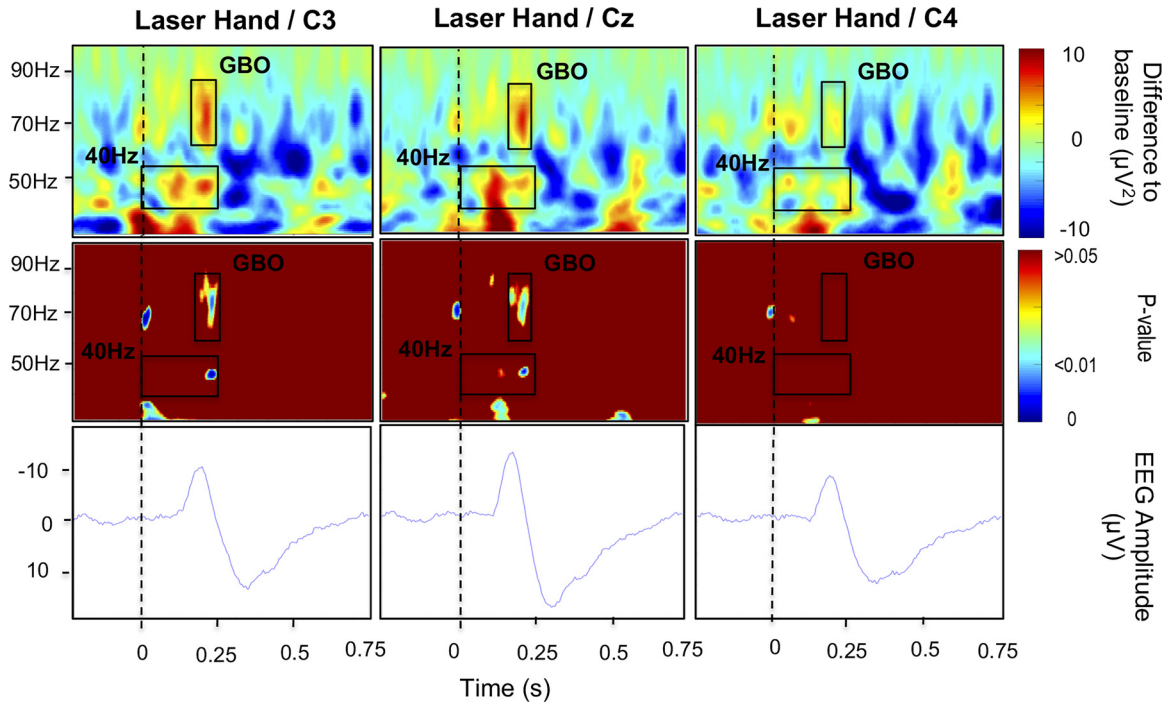

Fig. 5. Changes of time-frequency content and significance testing following nociceptive laser stimulation (right hand). The increase in high-frequency gamma power visible at *top* at electrodes C3 and Cz is matching a circumscribed significant increase in the same region of interest (*middle*). For comparison with standard measures, the N2P2 laser-evoked potential response (time domain) is shown at the *bottom*. GBO, gamma-band oscillation.

ing the evoked delta/theta-activity and the stimulus intensity yielded similar findings for nociceptive intensity coding (high versus medium laser intensity, $P < 0.001$, t test, $d' = 0.85$; medium versus low laser intensity, $P < 0.05$, t test, $d' = 0.89$; high versus low laser intensity, $P < 0.001$, t test, $d' = 1.67$) with increasing power together with an increase in stimulus intensity (Fig. 9*C*). This was not the case for the delta/theta response following tactile stimulation, where no comparable intensity coding could be verified (Fig. 9*D*). For tactile stimulation, no increase was found for either low or high-frequency activity within the two ROIs in the gamma band for tactile stimulation (Fig. 9, *F* and *H*). On the contrary, there even was a decrease of activity in the gamma band following tactile stimuli, which did not indicate intensity coding. This opposite change of GBO induced by nociceptive versus tactile stimuli was substantiated by the results of the two-factorial ANOVA (main factors stimulus modality and stimulus location) where the factor "modality" (nociceptive versus tactile) was highly significant [$F(1,11)$: 16.55, $P < 0.001$; main factor location $F(1,11)$: 0.14, $P > 0.7$; interaction $F(1,11)$: 1.52, $P > 0.2$]. Last, we examined the relation between the early, high-frequency gamma-oscillation and nociceptive stimulus intensity. In contrast to the EP amplitude and the delta/theta-band activity, the overall poststimulus (whole time window) power in the high-frequency range decreased in comparison to the power of the prestimulus baseline (Fig. 3). However, in the prior defined ROI (Table 1) of the high-frequency gamma band, an increase of stimulus intensity resulted in a statistically significant increase of the early GBO power ($P < 0.05$, t test, adjusted for multiple comparison by Bonferroni–Holm correction, $d' = 0.8$; laser high-intensity versus laser low-intensity; Fig. 9*G*). The low-frequency gamma response (40 Hz) did not yield significant findings that would indicate intensity coding (Fig. 9*E*). Findings for foot stimulation were similar (Fig. 9, *I–P*), however, the post hoc test for intensity coding of the GBO did not reach significance (Fig. 9*O*), and tactile stimulation caused a graded decrease in GBO (Fig. 9*P*).

DISCUSSION

One of the first observations of EEG recordings in humans was that functional brain activation leads to a measurable increase of low voltage activity at higher frequencies (Adrian and Matthews 1934; Jasper and Carmichael 1935). During the first half of the 20th century, due to technical restrictions, it was very difficult to record and analyze high-frequency responses (>30–40 Hz), which is why EEG research focused mainly on low gamma-oscillations around the 40-Hz band (Crone et al. 2011). During the 90s varying authors identified non-phase-locked 40-Hz activity in different cortical areas like the motor cortex (Pfurtscheller et al. 1994), auditory cortex (Pantev 1995), and visual cortex (Tallon-Baudry et al. 1997). More recently, some authors started to focus not only on low-frequency gamma-oscillations, but especially on high-frequency (>40 Hz) gamma activity and its relationship to human nociceptive processing (Gross et al. 2007; Zhang et al. 2012).

In the present study, we used time-frequency analysis to investigate whether early, high gamma-oscillations can be seen as a correlate of localized nociceptive processing in the somatosensory cortex and whether there are differences between the characteristics of low and high gamma-oscillations. In terms of intensity coding, both tactile and nociceptive stimuli evoked phase locked brain activity of increasing amplitude with increasing stimulus intensity, while only nociceptive stimuli generated high GBOs, which also encoded stimulus intensity. The topography of the high GBOs was compatible with a

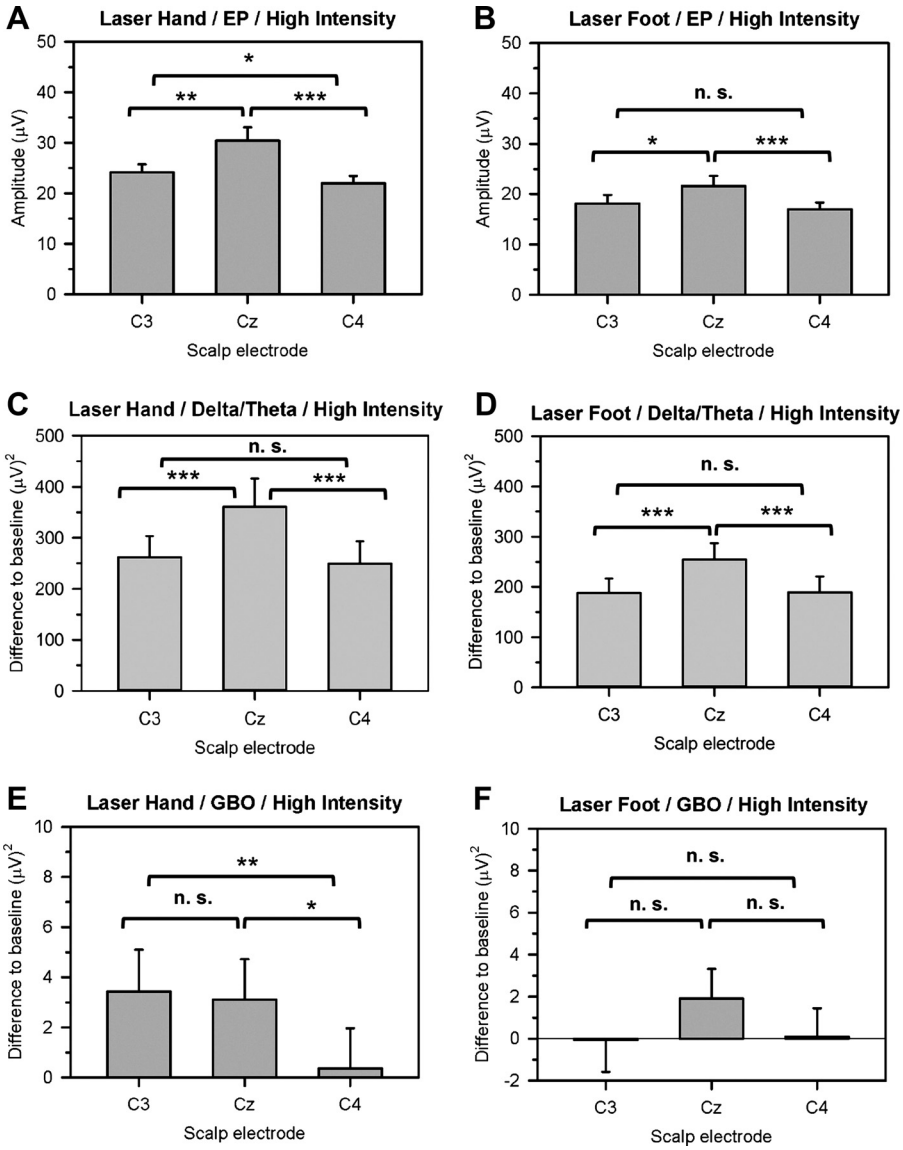

Fig. 6. Analysis of somatotopy, differences of the evoked potential (EP), delta/theta response, and the gamma-band oscillation (GBO) after nociceptive laser stimuli at the hand and foot at channels C3, Cz, and C4. Note the EP central vertex field distribution both after hand and foot stimuli (*A* and *B*). Low-frequency (delta/theta) oscillation revealed a similar spatial vertex pattern for both hand and foot stimulation (*C* and *D*). GBOs exhibited a leftward lateralized distribution for hand and a vertex distribution for foot stimulation (*E* and *F*). Data are presented as means ± SE, Student's paired-sample *t* tests. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; n.s., not significant; adjusted for multiple comparison by Bonferroni–Holm correction.

generation in the primary sensorimotor cortex, with maximum activity following hand stimulation at contralateral electrodes (C3) and maximum activity following foot stimulation at midline positions (Cz). Taking into account that high GBOs were coding (nociceptive) stimulus intensity and showed a characteristic topography after nociceptive stimuli, but were absent after tactile stimuli, high GBO at 65–85 Hz could be termed specific.

In this context, we also analyzed the role of the low gamma-oscillations around the 40-Hz band, when it comes to nociceptive processing in the somatosensory cortex, but found neither significant intensity coding nor a characteristic topography for the low-frequency gamma-oscillations making a specific role in somatosensory or nociceptive processing unlikely. We are aware of the existence of brief gamma bursts following tactile and/or electrical stimulation at the arrival of the first cortical volley (20–30 ms) in S1. These may code intensity (Huttunen 1995) and can occur at much higher frequencies (600 Hz; Curio et al. 1994; Gobbelé et al. 1998) far beyond our analysis window. Later, invasive recordings in epileptic patients yielded early cortical gamma responses at 15–17 ms following median nerve stimulation initiating in S1 at high frequencies beyond 100 Hz, spreading to M1 with lower frequencies toward 100 Hz (Fukuda et al. 2008). This might indicate that the highest frequency marks the initial (cortical) arrival of a sensory signal with subsequent feedforward distribution to neighboring and distant regions of the brain. Based on animal and human data, mainly from the visual cortex, a current concept comprises that the initial signal reaches superficial cortical layers (II and III) where high-frequency (gamma) rhythms are elicited as feedforward signal, probably through rhythmic GABAergic inhibition by interneurons (Cardin et al. 2009) whereas feedback signals to the same cortical columns or modules use lower frequencies (alpha or beta) in deeper layers (Fries 2015; Michalareas et al. 2016; see Bastos et al. 2012 for review). In that fashion, feedforward and feedback loops of information processing may locally and in distant regions combine processing modules through e.g., neuronal cross-frequency and/or cross-regional coupling. Even within gamma, there are subbands serving different functions of information transmission across various hierarchic areas of (visual) sensory processing (Tallon-Baudry 2009). The primary concept behind this may be that

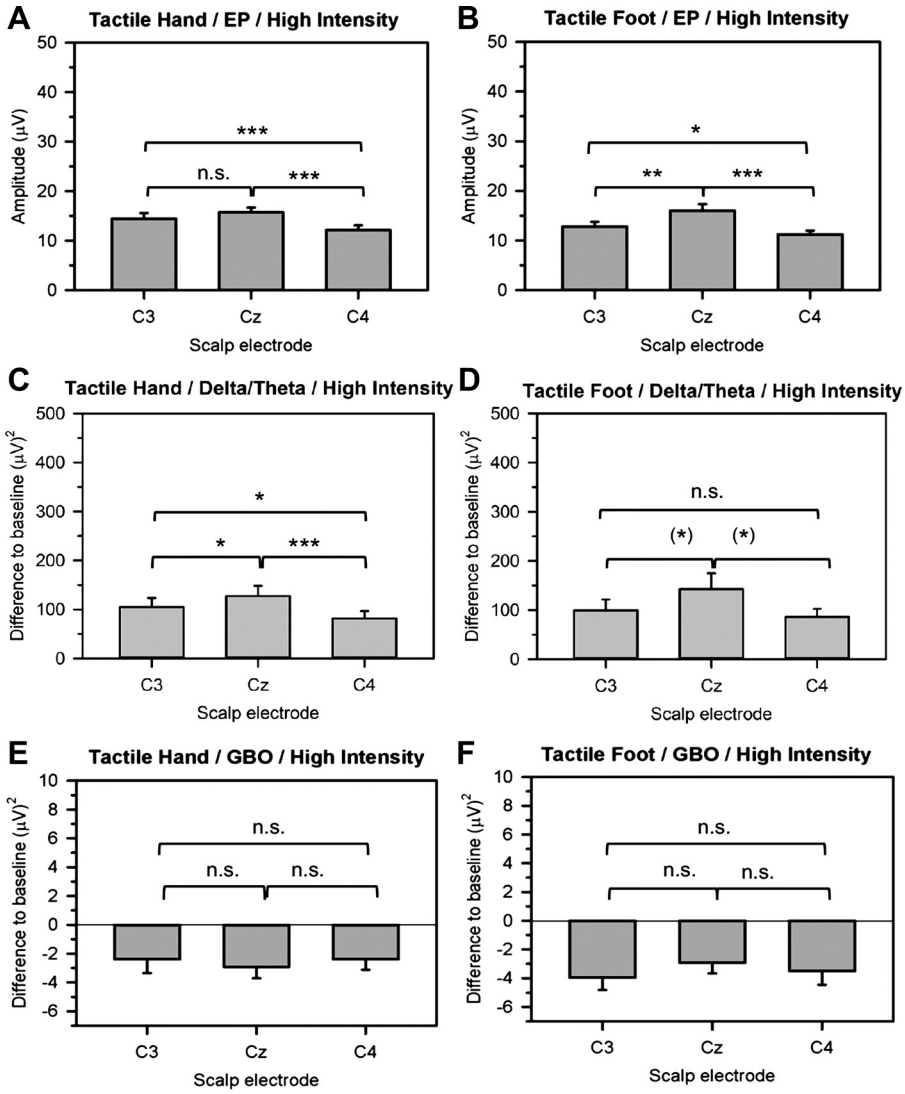

Fig. 7. For analysis of somatotopy, we examined differences of the evoked potential (EP), delta/theta response, and the gamma-band oscillation (GBO) after pneumatic stimuli at the hand and foot at channels C3, Cz, and C4 to look for lateralized or vertex-centered responses. The EP amplitudes showed a central vertex field distribution both after hand and foot stimuli (*A* and *B*). The analysis for the region of interest containing the delta/theta oscillation revealed a similar spatial vertex pattern for both hand and foot stimulation (*C* and *D*), whereas pneumatic stimuli induced decreases of activity in the region of early, high-frequency GBO. Data are presented as means ± SE, Student's paired-sample *t* tests. $*P < 0.1$; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; n.s., not significant; adjusted for multiple comparison by Bonferroni–Holm correction.

these mechanisms lead to fast binding of information, which results in an actual/new meaning with the consequence of a behavioral response. Since nociception is highly relevant in this respect, it would not be surprising if there were similarities in this complex hierarchical and parallel processing in the pain domain.

Topography of phase locked and non-phase-locked responses. Our results show that early 65- to 85-Hz gamma-oscillations induced by noxious stimuli generated brain activity with a topography well compatible with generation in the primary somatosensory cortex. Topography differed when stimuli were applied to the hand or foot: Laser stimuli of high intensity had the strongest gamma response at central, contralateral electrode location (C3) for stimuli applied at the right hand, significantly stronger than ipsilateral to stimulation (C4). Following foot stimulation, the gamma response was greater at the vertex (Cz) compared with both central, lateral hemispheres (C3 and C4). Previous studies used hand stimulation with laser or thermode stimuli only and found partly contradictory results. Whereas a number of studies found an early lateralized gamma response between 50 and 100 Hz contralateral to the stimulated hand following phasic stimuli (Gross et al. 2007; Hauck et al. 2007; Zhang et al. 2012) compatible with generation in sensorimotor cortex, the same and other authors found frontal medial early gamma responses (Schulz et al. 2011), responses at a later time (Hauck et al. 2007), by using tonic stimuli (Nickel et al. 2017) or at longer latencies in the low-frequency gamma range (40 Hz) without lateralization (Chien et al. 2014). These differences may be due to recording methods with different sensitivity to detect currents of different orientation (EEG versus MEG), the duration of the stimulus (phasic versus tonic) with different impact on affective load and/or saliency, or because of different analysis techniques.

Nociceptive processing in S1 in general has been demonstrated by noninvasive recording using phase-locked evoked potentials or fields (Kanda et al. 2000; Ohara et al. 2004a; Ploner et al. 2000; Schlereth et al. 2003; Tarkka and Treede 1993; Valentini et al. 2012) as well as invasive recordings (Baumgärtner et al. 2011; Frot et al. 2013). Although nociceptive neurons in S1 are sparse (Kenshalo and Isensee 1983), and activation of the S1 region in nociceptive tasks is less frequent than in other regions, like, e.g., the insula (Apkarian et al. 2005), a somatotopic representation in S1 also for nociceptive stimuli is likely (Bingel et al. 2004; Mancini et al. 2012).

To make sure our recording and analysis methods yielded plausible results in principle, the topography of the phase-

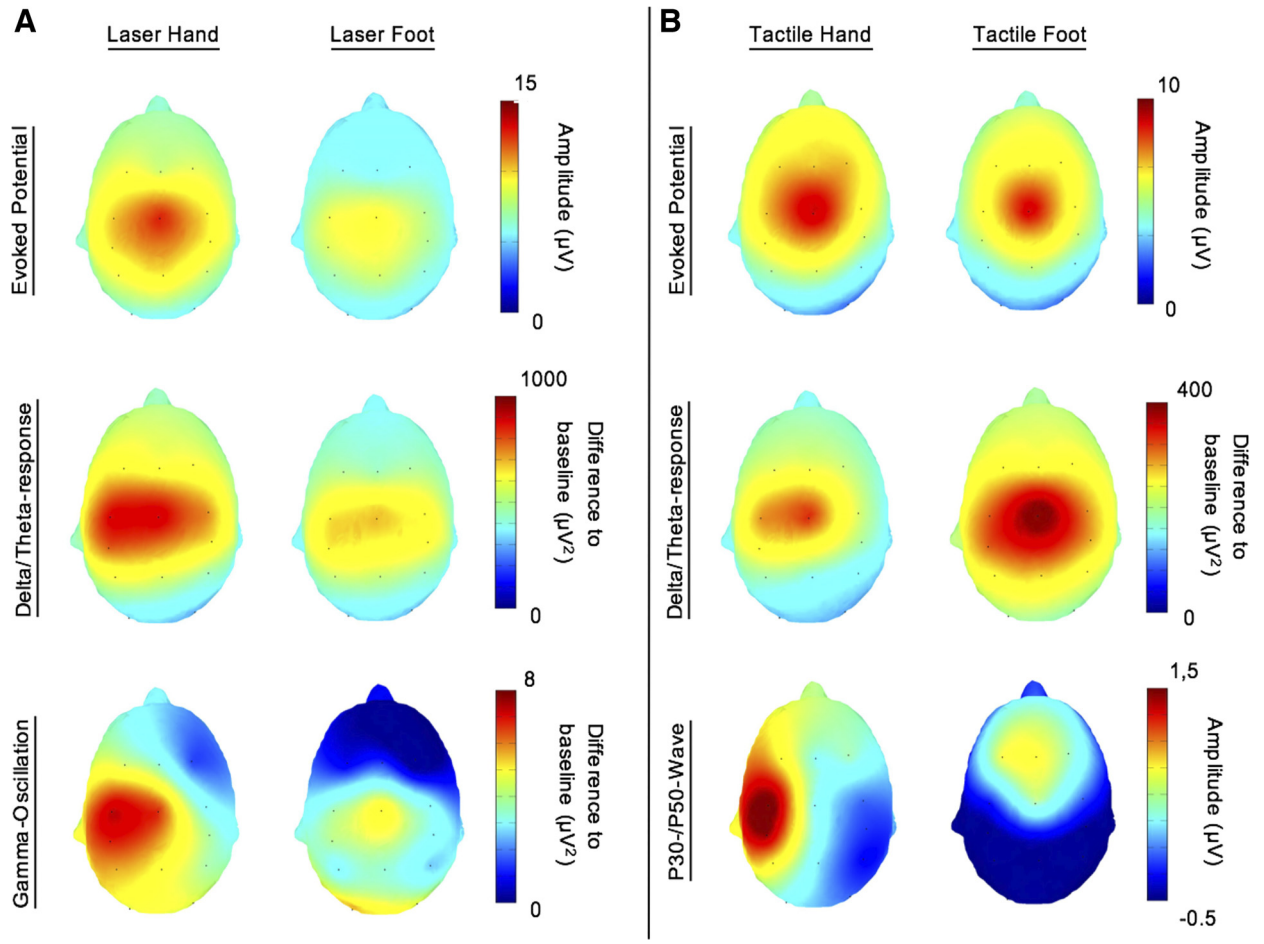

Fig. 8. Surface maps to illustrate somatotopy of the different responses elicited by nociceptive laser (*A*) and tactile stimuli (*B*). *A*: positivity of the biphasic N2P2 evoked potential (EP) response (*top*), power in the delta/theta band (*middle*), and power in the high-frequency gamma range [gamma-band oscillation (GBO); *bottom*]. Note especially the difference between the spatial pattern of the GBO after painful stimulation at the hand and foot. *B*: the late EP (*top*) and delta/theta response show central vertex somatotopies for hand and foot stimulation. The early somatosensory responses served as control and showed a lateralized response for hand stimulation (correlate of the electrical N20/P30). Note the similarity of surface patterns of laser-induced GBOs and the early tactile EP.

locked EEG responses by means of evoked potential amplitude was analyzed as well: The late potentials yielded a central distribution for both hand and foot stimuli as described in earlier reports with maximum amplitude at Cz with decay in symmetric circular direction as known for the N2-P2 LEP vertex amplitude both for the nociceptive as well as for the late vertex response following the tactile stimulus. Its correlate in the time-frequency domain, the low-frequency delta/theta response, also did not show differences in topography between hand and foot stimulation for either modality with a maximum amplitude at the vertex. In contrast, the early response of the tactile stimulus was clearly lateralized for the hand and centrally distributed for foot stimulation as correlate of the early S1 activity known as the median nerve N20 or P30 and tibial nerve P40. These findings indicate that amplitude and topographies of the late phase locked evoked responses do not directly coincide with high-frequency (65–85 Hz) gamma in terms of topography although the timing is similar, suggesting they are separate phenomena.

Specificity of GBO in the context of nociception. With respect to specificity of the gamma response for nociceptive stimuli, we found for both hand and foot stimulation not increased but rather decreased activity for tactile stimuli, whereas nociceptive stimuli led to a significant increase, well defined in terms of time and frequency range. Hence the GBO could be termed specific. A number of issues may challenge this conclusion: *1*) intensity coding in general, *2*) attention or salience effects, *3*) confounding artifacts like muscle activity. Intensity was initially matched between tactile and laser stimuli, since intensity ratings within both modalities were similar. Attention is increasing the magnitude of the phase-locked and non-phase-locked responses (Chien et al. 2014; Legrain et al. 2002; Schlereth et al. 2003). Since the tactile stimuli were perceived clearly, attention was drawn toward the stimulated hand, especially since subjects had to give ratings. Hence, a complete suppression of gamma increase during tactile stimulation due to attentional effects is unlikely. Saliency is hard to control for, and although the intensity within the modalities was similar as used in a previous attempt to control for saliency (Liberati et al. 2016), a painful stimulus will surely be more salient than a tactile stimulus. Thus saliency (and attention) effects on the magnitude of gamma are not just possible, but even probable. This could explain the magnitude of the response, or even presence or absence. In another study on oscillatory activity, Chien and coworkers (Chien et al. 2014) compared nociceptive laser and electrical stimuli (as tactile control) and tried to control saliency by focusing attention toward or away from the stimuli. They found attentional

Table 2. *Results of 2-factorial ANOVAs for the main factors stimulus location (limb; hand/foot), electrode (scalp electrode C3, Cz, C4), and interaction as well as F-values and P values and effect sizes (both global and partial η^2)*

Parameter	Factor	*F*-Value	*P* Value	Global η^2	Partial η^2
GBO—Laser high	Location	$F(1,11) = 1.31$	0.2769	0.0367	0.106
	Electrode	$F(2,22) = 6.20$	**0.0233**	0.0477	0.360
	Location*Electrode	$F(2,22) = 5.36$	**0.0127**	0.0251	0.328
GBO—Tactile	Location	$F(1,11) = 0.66$	0.4326	0.0208	0.056
	Electrode	$F(2,22) = 0.28$	0.690	0.0015	0.025
	Location*Electrode	$F(2,22) = 1.80$	0.1948	0.0112	0.140
Delta/Theta—Laser high	Location	$F(1,11) = 8.02$	**0.0163**	0.0837	0.422
	Electrode	$F(2,22) = 29.35$	**0.0001**	0.0858	0.727
	Location*Electrode	$F(2,22) = 8.75$	**0.0016**	0.0053	0.443
Delta/Theta—Tactile	Location	$F(1,11) = 0.12$	0.7374	0.0011	0.010
	Electrode	$F(2,22) = 12.55$	**0.0012**	0.0733	0.533
	Location*Electrode	$F(2,22) = 1.03$	0.3522	0.0035	0.085
EEG-Amp—Laser high	Location	$F(1,11) = 19.52$	**0.0010**	0.2264	0.640
	Electrode	$F(2,22) = 24.43$	**0.0001**	0.1716	0.689
	Location*Electrode	$F(2,22) = 9.81$	**0.0052**	0.0172	0.471
EEG-Amp—Tactile	Location	$F(1,11) = 0.46$	0.5240	0.0125	0.040
	Electrode	$F(2,22) = 25.95$	**0.0001**	0.2052	0.702
	Location*Electrode	$F(2,22) = 3.50$	0.0607	0.0144	0.241

Significant *P* values (below the level of $P = 0.05$) are marked in boldface.

modulation mainly at a late (later than 500 ms poststimulus) and long-lasting time window (up to 1,500 ms) in the low gamma range (40–50 Hz) for laser stimuli, but no early response in the gamma range of 65–85 Hz like we did. However, the somatotopy found for laser stimuli in our study is hard to explain by just salience, which is an unspecific effect of arousal with multimodal origin.

Artifacts from muscle activity or eye movement (saccades) are known to show activity in the gamma band that can be difficult to separate from neuronal activity (Muthukumaraswamy 2013). In our data, eye movement artifacts were eliminated by ICA removal. We did not use the same method to subtract muscle activity by purpose, since there is no objective way to clearly separate the muscle broad band activity from gamma. We did monitor the ongoing EEG and removed EEG segments with increased EMG activity by visual inspection. We are confident that our gamma response is brain activity because *1*) the topography is not frontal or temporal (but central), and *2*) the early activity is not ranging across all frequencies but covers a more distinct range between 50 and 80 Hz.

We determined that the early gamma-oscillations were only induced by laser stimuli perceived as clearly painful. Since we could not find comparable oscillations after tactile nonpainful stimuli, which corresponds to observations from previous studies pointing into the same direction (Gross et al. 2007; Schulz et al. 2012, 2015; Zhang et al. 2012), we can assume that early gamma-oscillations may appear as a correlate of localized nociceptive processing (Chien et al. 2014; Gross et al. 2007; Michail et al. 2016; Zhang et al. 2012). Another study also reported intensity coding in the primary sensorimotor cortex in the gamma range for electrical stimulation ranging from nonpainful to painful intensities (Rossiter et al. 2013), which would challenge the assumption of specificity. However, since electrical stimuli of that type typically excite both tactile and nociceptive afferents (Mouraux et al. 2010), the effect on cortical responses may also be mixed. Recently, Hu and Iannetti (2019) demonstrated in a large subject sample (>100) that high-frequency GBOs correlated well with subjective pain intensity, which is in accordance with our results. They furthermore could demonstrate that GBOs explained the subjective variability of pain perception within subjects (high versus low intensity laser stimuli), as a number of other measures did, too (both time-locked and non-time-locked responses), but also between subject variability (sensitive versus less sensitive subjects). In the same study, electrical stimuli also elicited GBO responses, although of smaller amplitude/power. The difference with respect to our finding of no response or even suppression with tactile stimuli could lie in the (un)specificity of the electrical stimulus or, perhaps more likely, in the behaviorally higher relevance of an artificial, potentially aversive or threatening stimulus. The evidence from this interesting study and others rather points to GBOs as correlate of intensity and relevance of subjective perception (of pain) rather than a direct marker of nociceptive input. Rather than the occurrence of GBO as such but the specific spatial, temporal and spectral features together may be correlate of specificity.

The present observation of early gamma-band oscillation induced by noxious stimuli being primarily generated in a cortical area overlapping with the somatosensory cortex and having the maximum amplitude at the central electrode contralateral to the stimulated hand is in agreement with most of the recent studies dealing with a similar topic (Hauck et al. 2007; Tiemann et al. 2010; Timmermann et al. 2001; Zhang et al. 2012). In one study (Nickel et al. 2017), results indicated that GBOs are mainly induced in the prefrontal cortex and did not show a different spatial distribution for GBO after noxious stimulation at the left and right hand. Their stimulus was tonic; a lateralized response following hand stimulation was observed for low-frequency activity in the alpha band.

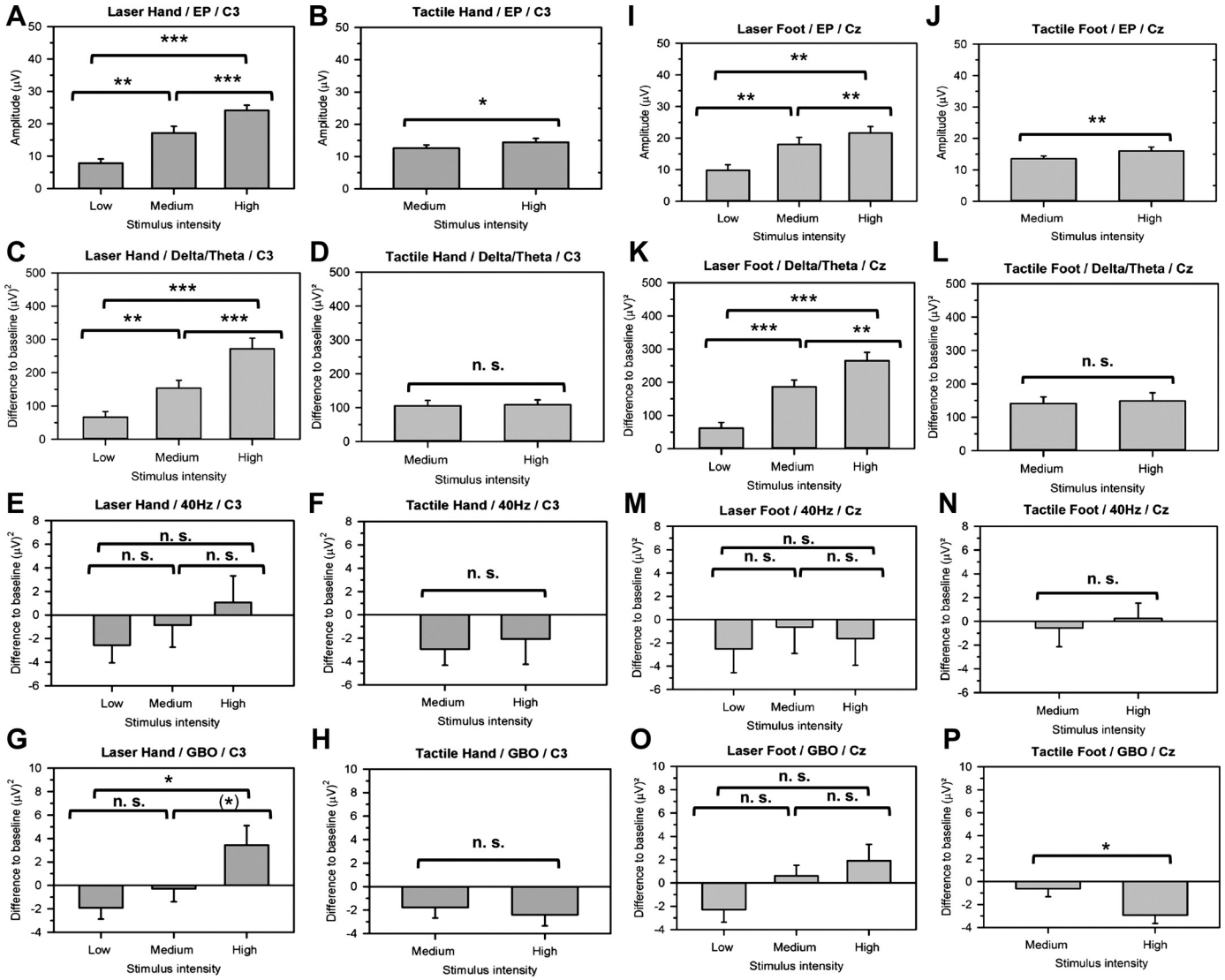

Fig. 9. Intensity coding of the evoked potentials and responses in the regions of interest (ROIs) containing the delta/theta oscillation, the 40-Hz band, and the gamma-band oscillation when stimulated at the right hand (*A–H*) and right foot (*I–P*) for both laser stimuli and pneumatic stimuli. For stimulation at the hand results are shown from the contralateral side (C3; *A–H*) and the central vertex for stimulation at the right foot (Cz, *I–P*). Evoked potential (EP) amplitudes increased both at C3 for hand stimulation and Cz for foot stimulation with stimulus intensity for laser as well as for pneumatic stimuli (*A*, *B*, *I*, *J*). Delta/theta oscillation only showed significant intensity coding for laser stimuli (*C*, *D*, *K*, *L*). The power in the 40-Hz-band for hand and foot stimulation did not show significant intensity coding neither for nociceptive nor tactile stimuli (*E*, *F*, *M*, *N*). Power in the ROI containing high-frequency gamma-band oscillation (GBO) showed statistically significant intensity coding between high and low laser intensity, a statistical trend between high and medium laser intensity, and decreases without intensity coding for tactile stimuli for hand stimulation (*G* and *H*). For foot stimulation only the tactile stimuli showed a significant difference; in opposite direction (*O* and *P*). Data are presented as means ± SE, Student's paired-sample *t* tests. $*P < 0.1$; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; n.s., not significant; adjusted for multiple comparison by Bonferroni–Holm correction, when three values were compared.

The probable assignment of GBO activity to S1 as one of the cortical regions for nociceptive processing is in agreement with previous studies using functional imaging and EEG and MEG recordings (Coghill et al. 1999; Ohara et al. 2004b; Ploner et al. 2000; Tarkka and Treede 1993) and meta-analyses of processing of phasic experimental pain (Apkarian et al. 2005; Garcia-Larrea et al. 2003), including more recent studies on information flow to S1 and fine grained somatotopy (Liang et al. 2013; Mancini et al. 2012). Since our focus was mainly on the gamma band, we did not analyze time-locked EP responses in more detail. The vertex distribution of the late EP following laser stimulation in our study for both hand and foot stimuli seems to contradict findings by, e.g., Valentini and coworkers, who did find a lateralized response for laser stimuli following hand stimulation. This was evident for the laser component N1, which precedes the N2P2 response described in our study (Valentini et al. 2012). The generator of the N1 is likely to be a combination of brain areas S1 and the operculoinsular cortex, whereas the later N2P2 is generated in the mid cingulate (for review see Garcia-Larrea et al. 2003). Recent invasive recordings from the insula from epilepsy patients receiving multimodal stimuli demonstrated that local field potentials of similar amplitudes occurred at the same contacts in anterior and mid insula following nociceptive as well as nonnociceptive stimuli, rendering these responses unlikely to be specific for nociception (Liberati et al. 2016). On the other hand, in a follow-up study, in contrast to local field potentials, GBOs were primarily elicited following laser stimuli, whereas no clear GBOs, or less

Table 3. *Three factorial repeated-measures ANOVA for the main effects of stimulation intensity, electrode and stimulus location (hand, foot)*

		Laser Stimulation				Tactile Stimulation			
	Effect	df	*F*	ges	*P* value	df	*F*	ges	*P* value
					GBO				
1	Energy	1.58, 17.33	7.54**	0.14	0.007	1, 11	3.45†	0.06	0.09
2	Electrode	1.25, 13.75	6.41*	0.01	0.02	1.39, 15.27	10.09	0.005	0.34
3	Limb	1, 11	1.64	0.01	0.23	1, 11	00.00	<0.0001	0.95
4	Energy:Electrode	2.54, 27.94	2.75†	0.01	0.07	1.46, 160.09	0.28	0.001	0.69
5	Energy:Limb	1.76, 19.38	0.42	0.008	0.64	1, 11	0.91	0.02	0.36
6	Electrode:Limb	1.14, 12.58	0.93	0.005	0.37	1.73, 190.04	4.49*	0.02	0.03
					40-Hz Oscillations				
1	Energy	1.31, 14.41	1.21	0.02	0.31	1, 11	0.93	0.005	0.36
2	Electrode	1.47, 16.20	0.82	0.004	0.42	1.91, 21.02	4.16*	0.02	0.03
3	Limb	1, 11	3.88†	0.01	0.07	1, 11	0.01	0.0001	0.94
4	Energy:Electrode	1.47, 16.15	0.53	0.003	0.54	1.14, 12.51	2.70	0.01	0.12
5	Energy:Limb	1.41, 15.51	0.68	0.01	0.47	1, 11	0.53	0.005	0.48
6	Electrode:Limb	1.59, 17.44	1.68	0.003	0.22	1.34, 14.74	1.41	0.005	0.26
					0.3- to 7-Hz Oscillations				
1	Energy	1.63, 17.94	18.61***	.36	<0.0001	1, 11	00.01	<0.0001	0.92
2	Electrode	1.94, 21.34	32.33***	0.08	<0.0001	1.58, 17.34	16.34***	0.08	0.0002
3	Limb	1, 11	8.61*	0.05	0.01	1, 11	0.07	0.0004	0.79
4	Energy:Electrode	2.61, 28.67	9.89***	0.01	0.0002	1.44, 15.83	1.06	0.0009	0.35
5	Energy:Limb	1.42, 15.61	2.12	0.01	0.16	1, 11	0.06	0.0002	0.82
6	Electrode:Limb	1.39, 15.33	10.14**	0.004	0.003	1.23, 13.49	1.01	0.003	0.35
					Evoked Potential				
1	Energy	1.31, 14.43	34.04***	0.046	<0.0001	1, 11	17.24**	0.07	0.002
2	Electrode	1.39, 15.31	22.64***	0.09	<0.0001	1.57, 17.30	36.21***	0.22	<0.0001
3	Limb	1, 11	9.19*	0.05	0.01	1, 11	1.29	0.03	0.28
4	Energy:Electrode	1.82, 20.01	9.93**	0.02	0.001	1.73, 19.05	0.66	0.0008	0.51
5	Energy:Limb	1.58, 17.43	8.00**	0.06	0.005	1, 11	0.55	0.002	0.47
6	Electrode:Limb	1.41, 15.49	7.78**	0.005	0.008	1.56, 17.21	1.78	0.007	0.20

ges, Total etha square. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. †$P < 0.1$.

increase in gamma power, was observed after visual, auditory, or tactile stimuli (Liberati et al. 2018b), suggesting that GBOs might be specific for nociception, or at least thermoreception in the insula (Craig et al. 2000). More recent data from the same group showed that the GBO increase recorded from mostly anterior and mid insular contacts was less following repetitive application (train of 3 stimuli every second) of laser pulses, indicating that even these responses habituate while perception does not (Liberati et al. 2018a). Whether these finding can be alluded to the sensorimotor cortex is yet unknown, but not unlikely.

Two recent studies in rodents are important in underlining the role of S1 in nociception/pain and GBOs. Out of a number of laser or pain-related brain responses, only GBOs were correlated with pain-related behavior (Peng et al. 2018). More recently, Tan and coworkers demonstrated an involvement of gamma in S1 on a different level (Tan et al. 2019). They found increased gamma activity of S1 cortex immediately preceding nocifensive (withdrawal) behavior after mechanical paw stimulation. In addition, ongoing gamma activity was increased in an inflammation model, and the withdrawal frequency as well as the gamma increase stronger in the inflamed condition. The authors then optogenetically stimulated inhibitory neurons with the consequence of increasing the gamma power in S1. With entrainments of both 40 Hz and 80 Hz, animals became hypersensitive to mechanical stimuli (lower withdrawal thresholds, higher withdrawal frequencies to given intensities). This was not the case for lower stimulation frequencies (e.g., theta) or when stimulating the primary motor area M1 (Tan et al. 2019). These findings support our findings suggesting that gamma oscillations in the somatosensory cortex play a special role in nociception as well as pain or pain-related behavior (in animals) and the underlying neural pathways.

Decreases in gamma power. One observation which was previously not described systematically, is the reduction of gamma activity (or gamma desynchronization) following tactile stimuli or a longer lasting suppression in general also following nociceptive stimuli (apart from the circumscribed increase following the nociceptive stimulus). In a recent study, an increase was described following somatosensory electrical stimulation, whereas there was no clear change in gamma following auditory or visual stimulation (Hu and Iannetti 2019). Since in our data there is no somatotopy for tactile gamma desynchronization and unclear intensity coding (decrease; main effect as a trend; post hoc just significant for foot) the effect does not seem to be specific. Other studies found decreases in power in the alpha and beta frequency bands following tactile stimuli in part with a beta rebound (Cheyne et al. 2003; Schweitzer et al. 2001). In a recent report using MEG (Andersen and Lundqvist 2019), repeated tactile stimulation of a finger led to the well-known time-locked responses in SI and SII, but at the same time to circumscribed brief decreases in the alpha- and beta ranges in the primary sensorimotor region (followed by a rebound). Since the authors did not focus on GBOs specifically (no ROI analyses), the smaller effects on GBO suppression could have been hidden. Omission of stimuli

led to time-locked activity in the operculoinsular cortex, and the first reoccurring tactile stimulus after the omission activated the anterior insula in the gamma range. Stimulus-evoked brief gamma responses might be a tag for behaviorally relevant information, inducing a tonic inhibitory response.

Limitations. Our exploratory study has a number of limitations, calling for some caution in making too strong statements. First, the number of 12 subjects might be considered to be borderline low. However, effect sizes for the occurrence/existence of GBOs were high ($d = 0.8$ and beyond, indicating sufficient power). The effect sizes for the somatotopy differences were only low to moderate ($d = 0.3–0.4$). With small sample sizes, however, effect sizes may not be estimated correctly (Button et al. 2013), and validation by replication would be desirable. Second, the intensity matching between nociceptive and nonnociceptive stimuli was not ideal, since we applied three nociceptive and two tactile intensities. By matching the two suprathreshold intensities of the laser with the two tactile (suprathreshold) intensities we left out the lowest (threshold) nociceptive intensity to avoid floor effects. Since the main reason for the matching was to account for saliency, we (if at all) overestimated the effect of saliency for laser stimuli. Second, we did record a relatively low number of channels since we initially had a direct focus of interest on the S1 region and the question of lateralization. Although the channels covered the scalp from frontal to occipital including lateral regions, a clear assignment to e.g., primary motor or primary sensory cortex is not possible with this spatial resolution, and hence, no reliable source analysis. Future work should be aiming to analyze also deeper brain regions in source space. Nevertheless, conclusions can already be drawn from our present findings based on surface field analyses that may stimulate further investigations.

Our finding that the exclusive appearance of early gamma-oscillation after noxious stimuli may indicate that early gamma-oscillations may be a specific correlate of localized nociceptive processing in the somatosensory cortex, is part of an ongoing debate about the role of GBO with during nociception and/or pain processing. Our results are in accordance with recent studies proposing that GBO could be a direct correlate of subjective pain perception (Gross et al. 2007; Michail et al. 2016; Zhang et al. 2012) adding specific information on somatotopy by directly comparing hand and foot stimulation and increasing specificity of real tactile stimuli in contrast to previously used electrical stimuli. In line with these findings in human studies, in a recent study in rodents, out of a number of laser-pain induced changes of brain responses, only GBO were correlated with pain-related behavior (Peng et al. 2018).

However, it is important to note that GBOs have already been reported in other cortical areas than the somatosensory cortex (Mann et al. 2005; Pinault and Deschênes 1992; Sirota et al. 2008; Tort et al. 2008) and were also evoked by non-painful stimuli (Başar et al. 2001; Yuval-Greenberg et al. 2008). Therefore, the specificity of GBO surely cannot be true in a general meaning, but more likely under certain conditions that need to be specified, like attentional-behavioral context (Schulz et al. 2011; Tiemann et al. 2010) and stimulus characteristics (Chien et al. 2014; Nickel et al. 2017) when nociception is involved.

Conclusions. Our results show that the early and brief gamma-response in the high-frequency range is induced by phasic noxious stimuli, not by nonnociceptive tactile stimuli. This early gamma-oscillation is likely to be generated, at least in part, within S1 with lateralized versus vertex-oriented somatotopies for hand and foot stimuli. The specific spatial and temporal-spectral features of this response may constitute its specificity. Due to its characteristic intensity coding and spatial distribution induced by nociceptive stimuli only, the recorded early gamma-oscillations may be identified as part of the lateral somatosensory system processing sensory discriminative aspects of the stimulus. These findings contribute to the debate about the specificity of high GBO for pain perception and extend the understanding of the spatial distribution of early gamma-oscillations.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.H. performed experiments; C.H., A.M., and U.B. analyzed data; C.H., A.M., and U.B. interpreted results of experiments; C.H. prepared figures; C.H. drafted manuscript; C.H., A.M., R.-D.T., S.S.-H., A.R., and U.B. edited and revised manuscript; C.H., A.M., R.-D.T., S.S.-H., A.R., and U.B. approved final version of manuscript; R.-D.T. and U.B. conceived and designed research.

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