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**Facial expressions of pain
modulate observer's long-latency STS responses**

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Abstract

The strength of brain responses to others' pain has been shown to depend on the intensity of the observed pain. To investigate the temporal profile of such modulation, we recorded neuromagnetic brain responses of healthy subjects to facial expressions of pain. The subjects observed grayscale photos of the faces of genuine chronic pain patients when the patients were suffering from their ordinary pain (*Chronic*) and when the patients' pain was transiently intensified (*Provoked*). The cortical activation sequence during observation of the facial expressions of pain advanced from occipital to temporo-occipital areas, and it differed between *Provoked* and *Chronic* pain expressions in the right middle superior temporal sulcus (STS) at 300–500 ms: the responses were about a third stronger for *Provoked* than *Chronic* pain faces. Furthermore, the responses to *Provoked* pain faces were about 40% stronger in the right than the left STS, and they decreased from the first to the second measurement session by one fourth, whereas no similar decrease in responses was found for *Chronic* pain faces. Thus, the STS responses to the pain expressions were modulated by the intensity of the observed pain and by stimulus repetition; the location and latency of the responses suggest close similarities between processing of pain and other affective facial expressions.

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Introduction

Why do we give a grimace of pain when we see other people getting injured? We cannot have the same sensory experience of pain as the person we are observing, yet we seem to have an immediate insight into what is happening—even in the absence of a verbal report. Since the observer receives no direct noxious input and no conscious efforts are needed, the insight seems to stem from the observer’s own experiences that enable sharing a part of the affective experience of the person in pain. Indeed, the brain research of the past decade has demonstrated that the observer’s own emotion- and movement-related brain areas are activated during mere perception of actions or affective states of another person [for reviews, see Frith and Frith, 2006; Hari and Kujala, 2009; Rizzolatti et al., 2001].

Similarly, observing or imagining someone else’s pain recruits the affective pain network, especially the anterior cingulate cortex (ACC) and the anterior insula (AI), in both subject’s and observer’s brain [Botvinick et al., 2005; Jackson et al., 2005; Morrison et al., 2004; Saarela et al., 2007; Singer et al., 2004]. This cortical circuitry relates to the unpleasant feeling one associates with pain [for a review, see Rainville, 2002]. Moreover, the functional magnetic resonance imaging (fMRI) response of the observer’s AI correlates positively with the intensity of the observed pain [Saarela et al., 2007]. These results suggest that the ability to understand the internal states or “feelings” of others’ pain is supported by a brain network that is activated both when people experience pain and when they observe pain in someone else. Similar brain mechanisms for shared sensory-affective experiences in humans have been found also for touch [Avikainen et al., 2002; Keysers et al., 2004] and disgust [Krolak-Salmon et al., 2003; Wicker et al., 2003].

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Until now, the majority of brain imaging studies on witnessing others' pain have focused on measuring the relatively slow cerebral haemodynamics. However, both real-life events and cortical processes have a characteristic temporal organization, and the corresponding rapid time courses can be tracked in the human brain with time-sensitive electrophysiological methods. Time scales of 50–250 ms characterize many types of perceptual and cognitive phenomena, such as sensory integration, figure–ground segregation, and object categorization and recognition. Following the time course is of particular interest when a neuron population processes different aspects of sensory information in different time windows; for example, the earliest visual responses of neurons in the monkey middle superior temporal sulcus are modified by the coarse shape of faces (related to e.g. species), but the detailed information (such as identity) affects the neurons' responses 50 ms later [Sugase et al., 1999].

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Also in the human brain, various aspects of facial information are processed in different time windows. Observing a face elicits the earliest prominent responses in the occipital visual cortices around 100 ms, which are mainly related to the low-level visual processing—although some face-specific processing possibly takes place also at these early latencies [Liu et al., 2002]. The temporo-occipital 170-ms responses (peaking at 140–200 ms in different studies) are clearly stronger to faces than to other visual categories [Allison et al., 1994], and they correlate strongly with face recognition performance [Tanskanen et al., 2005]. Subsequent processes around 200–500 ms show similar correlation with face recognition [Tanskanen et al., 2007], but unlike the 170-ms responses, they are also modulated by the subject's task [Furey et al., 2006; Lueschow et al., 2004] and the familiarity of faces [Paller et al., 2003].

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The long-latency cortical responses are also modulated by emotional expressions of faces. When subjects observe happy, disgusted, surprised or fearful faces, event-related EEG responses peak in the occipital and temporal regions 250–750 ms after the stimulus onset [Carretie and Iglesias, 1995; Krolak-Salmon et al., 2001]. Intracortical recordings indicate similar latencies for the reactivity of the human anterior insula, which responds to facial expressions of disgust at 300–500 ms [Krolak-Salmon et al., 2003], and to painful CO₂-laser stimuli already at 180–230 ms [Frot and Mauguiere, 2003].

To reveal the temporal dimensions of a shared pain experience, we recorded neuromagnetic brain responses from healthy subjects while they observed facial expressions of pain. The stimuli were photos of *Provoked* pain faces (chronic pain patients whose pain was transiently intensified) and *Chronic* pain faces (the same patients at rest); we were especially interested in the possible amplitude and hemispheric differences between responses to these pain expressions, as well as in the resilience of the responses to stimulus repetition. Furthermore, *Neutral* faces (gender-matched actors) and *Scrambled* images (all the face photos phase-randomized) were presented as control stimuli, with the aim to detect the general face-sensitive brain responses. Based on previous findings on pain and emotion, we hypothesized that the more intensive *Provoked* pain faces would recruit responses either in brain areas related to affective pain processing, or in brain areas involved in processing facial expressions of emotions.

Materials and methods

Subjects

Eleven healthy adults participated in the study but responses from 2 subjects were discarded due to excessive eye blinks. Thus, data from 9 subjects (6 females, 3 males; 26–40 years, mean \pm SD 29 ± 4 years) were analyzed. All subjects were right-handed according to the Edinburgh Handedness Inventory [Oldfield, 1971]: on the scale from -1 (left) to $+1$ (right), the mean \pm SEM score was 0.94 ± 0.03 (range from 0.8 to 1).

Participants of the MEG experiments gave their written, informed consent prior to the experiment, and a similar consent was also obtained from the chronic pain patients and actors before they were videotaped for the stimuli. The generation of the pain face stimuli and the MEG recordings had prior approvals by the ethics committee of the Helsinki and Uusimaa Hospital district.

Stimuli

The subjects were shown intact and scrambled (phase-randomized) grayscale still photos of faces that displayed *Provoked* pain, *Chronic* pain and *Neutral* facial expressions (Fig. 1), previously used in our fMRI study [Saarela et al., 2007]. We used real pain faces as stimuli, similarly as Botvinick et al. [2005], since acted facial expressions of pain can differ from genuine pain expression [Hill and Craig, 2004]. The facial photos expressing pain were obtained from four patients (2 females, 2 males) suffering from chronic pain; photos of *Chronic* pain when the patients were at rest and photos of *Provoked* pain when the patient's own pain was transiently intensified, e.g. by gently moving or stroking the painful limb. The preparation,

behavioral pre-testing, and selection of the pain face stimuli are described in detail in Saarela et al. [2007].

The *Neutral* faces were originally obtained from healthy gender-matched actors for another study [Schürmann et al., 2005], and re-used as control stimuli in our previous pain experiment [Saarela et al., 2007]. The *Neutral* faces depicted faces of two males and two females not showing any explicit emotion (see example in the Figure 1). The purpose of *Neutral* and *Scrambled* faces in this study was to aid in detecting general face-sensitive brain responses.

– Fig. 1 here –

Ratings of pain intensity

During filming the stimuli for our former study [Saarela et al., 2007], the pain patients, whose faces were shown in the current study, estimated their own pain once during the *Chronic* state and 3–5 times during the *Provoked* state. The mean pain estimates of the four patients were 3.9 for the *Chronic* state (7, 3, 2, and 3.5 by patients 1, 2, 3, and 4, respectively) and 8.9 for the *Provoked* state (8.7, 9, 8.1, and 6.9, respectively) on a scale from 0 (minimum) to 10 (maximum).

In our original behavioral stimulus selection study [Saarela et al., 2007], 25 different photos of 5 pain patients were shown (each for 2.5 s with an interval of 5 s) in a random order to 30 individuals who did not participate in the fMRI study; the subjects' task was to rate the facial expressions for pain intensity. As a result, 24 stimuli from 4 pain patients were selected for our original fMRI recordings [Saarela et al., 2007] and re-used here. This set of stimuli comprised 3 *Chronic* pain photos (with lowest ratings) and 3 *Provoked* pain photos (with highest ratings) from each patient. As was already stated in the original publication, the mean \pm SEM pain rating was 3.3

± 0.3 for the final set of *Chronic* pain photos and 6.7 ± 0.3 for the *Provoked* pain photos. Thus, the intensity ratings were slightly smaller but in good overall accordance with the ratings of the pain patients themselves.

For the current study, we re-analyzed the behavioral data to find out whether the subjects' pain intensity ratings were affected by repeated exposure to the pain expressions of the same patient. We first obtained the pain ratings of each patient's pain faces shown as the first and the last within the stimulation sequence, separately for *Provoked* and *Chronic* pain. In the subsequent repeated-measures ANOVA, pain intensity and stimulus repetition served as within-subjects factors, and ratings to the first and last photos of a patient were compared with planned contrasts.

Stimulus presentation and instructions

Stimulus presentation was controlled by the Presentation® software (<http://nbs.neuro-bs.com/>) running on a PC computer. The images were displayed on a rear projection screen by a data projector (VistaPro™, Christie Digital Systems Inc., Cypress, CA, USA). The experiments were run in the standard VGA mode (resolution 640 x 480 pixels, frame rate 60 Hz, 256 gray levels). The image size was 12.7 cm x 17 cm (width x height) on the screen, and the stimuli were viewed binocularly with moderate background illumination at a distance of 94 cm. The average stimulus luminance was 100 cd/m² for each stimulus category.

The photos were overlaid on a gray 30.5 cm x 23 cm (width x height) display area, luminance-matched with the mean of the face stimuli. Each stimulus was shown for 2 s, and the inter-stimulus interval was 2.0–2.5 s. The total number of different stimuli in the whole experiment was 12 for the *Provoked* pain faces, 12 for the *Chronic* pain faces, 24 for the *Neutral* faces, and 48 for the *Scrambled* faces (all the previous stimuli phase-randomized). Stimuli were presented in two subsequent

recording sessions in a pseudorandomized order, counterbalanced across subjects. During one recording session (duration approximately 18 min), all *Provoked* pain, *Chronic* pain and *Neutral* faces were presented 4 times, and the *Scrambled* faces once, resulting in 48 *Provoked*, *Chronic*, and *Scrambled* faces, and in 96 *Neutral* faces per recording session.

The subjects were informed that the stimuli contained neutral facial expressions, facial expressions of pain, and scrambled images. Subjects were instructed to view all the stimuli attentively, but no extra behavioral task was given.

MEG data acquisition

Neuromagnetic fields were acquired with a whole-scalp Vectorview system (Neuromag Ltd, currently Elekta Neuromag Oy, Helsinki, Finland) comprising 306 sensors: two orthogonal planar gradiometers and a magnetometer on each of the 102 triple-sensor elements. MEG signals were band-pass filtered to 0.1–170 Hz and digitized at 600 Hz. The responses were averaged from 200 ms before the stimulus to 1000 ms after the stimulus onset. For data analysis and source modeling, the responses were low-pass filtered at 40 Hz, and a pre-stimulus baseline of 200 ms was applied. Before averaging, trials contaminated with eye movements (detected from horizontal and vertical electro-oculograms) or excessive MEG signals were discarded.

Data analysis

Sensor-level analysis

For inspecting the sensor-level data, only the planar gradiometers were used since they pick up the strongest signals directly above local current sources. In each of the two recording sessions, ≥ 39 responses for each stimulus category were acquired (twice as many for *Neutral* faces).

Since individual variation in the cortical anatomy and in the head position with respect to the MEG sensors renders intersubject comparison of magnetic field pattern orientation questionable, we removed orientation information from the data by first calculating vector sums of the two orthogonal planar gradients for each sensor element and for each condition. Thereafter, we identified the channels that showed prominent responses for *Provoked* and *Chronic* pain faces. This search yielded five locations: right and left temporal cortices, occipital cortex, and right and left temporo-occipital cortices. At each of these five regions, the signals were spatially averaged over six channel pairs (see Fig. 3 for sample responses from subject S1 and for the locations of channels from which the signals were averaged in all subjects). Comparison of these areal averages across subjects simplifies the data analysis, since the signals from few adjacent channels are more stable than signals from single channels alone—this procedure has proven useful and robust in previous MEG analyses [e.g. Avikainen et al., 2003; Hari et al., 1997; Uusvuori et al., 2008]. A minor drawback is the decrease of the amplitude as a result of spatial averaging. Sensor-level areal averages were subjected to statistical testing with repeated-measures ANOVA, aimed to reveal possible effects and interactions of stimulus category, hemisphere, and measurement session. Subsequently, post-hoc comparisons were applied to reveal the origins of the observed differences.

Source modeling

To estimate the neural generators of the evoked responses, we modeled cortical sources of the responses from the first session to the *Provoked* and *Chronic* pain faces. Cortical current sources were estimated for 8 out of the 9 subjects; no structural magnetic resonance images were available for one subject (S9). First, the MEG data were spatially filtered by the Signal Space Separation method [Taulu et al.,

2004] to suppress external magnetic interference. Second, anatomical MR images were processed with the FreeSurfer software package [Dale et al., 1999; Fischl et al., 1999] to obtain cortical surface reconstructions; the border of white and grey matter was tessellated and decimated to a 7-mm grid of MEG source points (Fig. 2).

– Fig. 2 here –

Thereafter, cortically-constrained and noise-normalized minimum-norm estimates [MNEs, also referred to as dynamic Statistical Parametric Maps by Dale et al., 2000] were computed using the “MNE Software” package [developed by Matti Hämäläinen at Massachusetts General Hospital: Lin et al., 2006]. All 306 channels of the Vectorview MEG system were used for the analysis, and cortical current generators were modeled for the whole cortex.

Since the signals detected by MEG arise mainly from postsynaptic currents in the pyramidal neurons [see e.g. Hari, 1990; Okada et al., 1997], currents normal to the cortical surface were favored by applying a loose orientation constraint, which weights currents flowing along the cortex by a factor of 0.3 with respect to currents perpendicular to it. A single-compartment boundary element model of the inner skull surface served as the volume conductor for cortical currents. The noise covariance estimate required by the MNE was obtained from the unaveraged baseline periods (from –200 ms to 0 ms relative to stimulus onset) and was computed independently for all subjects. Subsequently, the responses were normalized relative to the noise level of the measurements, resulting in response strengths as z -scores [Dale et al., 2000].

For a group average, individual source estimates of *Provoked* and *Chronic* categories were first temporally smoothed by a ± 50 -ms moving average. The individual MNEs were then morphed to a standard atlas brain provided by the FreeSurfer package (“fsaverage”, an average of the brains of 20 healthy adults) with spatial smoothing. Subsequently, the morphed MNEs were averaged at 400 ± 50 ms across subjects and the results were visualized on the standard atlas brain.

The top panel of Fig. 6 shows the across-subjects statistical z-score maps; for closer group-level statistical comparisons of the cortical source strengths between *Provoked* and *Chronic* conditions, ellipsoidal regions of interest (ROIs) were selected post-hoc in the right and left STS of the atlas brain to cover the peak responses of the group data (see Fig. 6, top panel), and the peak amplitudes of the temporally-smoothed responses within 300–500 ms were measured from the ROI signal for each subject. The normalized amplitudes (z-scores) were compared for the effects of hemisphere and stimuli with repeated-measures ANOVA and paired-samples t-tests were used post-hoc to find the origins of the differences.

Results

Behavioral pain ratings

In the re-analysis of the pain ratings by 30 individuals in our previous study [Saarela et al., 2007], repeated-measures ANOVA revealed the main effects of both pain intensity and stimulus repetition on the pain ratings (repetition \times intensity; $p < 0.001$ for intensity and $p < 0.05$ for repetition). The planned contrasts showed 9% decrease of the pain ratings for *Provoked* pain faces from the first to the last photo of a patient (from 7.14 ± 0.16 for the first photo to 6.48 ± 0.17 for the last photo; $p <$

0.01, paired-samples t-test). The ratings of Chronic pain faces from the first to the last photo did not change (3.36 ± 0.15 for the first photo vs. 3.10 ± 0.15 for the last photo).

Spatial distributions, temporal waveforms and latencies of the responses

Fig. 3 shows the spatial distribution of the observed responses in a representative subject. In the occipital sensors, strong transient responses peaked at 112 ms to all stimuli, with the maximum amplitude around 110 fT/cm (Fig. 3a). Additional transient responses occurred in the right temporo-occipital sensors for all intact face stimuli (*Provoked*, *Chronic* and *Neutral* faces), peaking at 147 ms with an amplitude of about 90 fT/cm (Fig. 3b) and in the left temporo-occipital sensors at 143 ms with amplitude of about 85 fT/cm (Fig. 3c). Furthermore, a much slower deflection peaked around 300–500 ms in the temporal-lobe sensors, in both right (Fig. 3d) and left hemisphere (Fig. 3e). These long-latency responses were strongest for *Provoked* pain faces (represented by red curves in Fig. 3), with maximum amplitudes around 120 fT/cm. Responses in the central and frontal sensors were very weak for intact face photos.

– Fig. 3 here –

The analysis windows for data across subjects were 90–120 ms for occipital visual responses, 140–160 and 140–170 ms for the temporo-occipital “face responses” in the right and left hemisphere, respectively, and 300–500 ms for the late temporal-lobe responses (see Fig. 4).

Early responses in occipital and temporo-occipital regions

As expected, the response waveforms to *Scrambled* faces were clearly different from those to the other categories, sharing only the latency and form of the first visual response (at 90–120 ms in the occipital cortices) with other stimulus categories (Fig. 3a). A small stimulus effect was observed in these occipital responses (stimulus \times session, stimulus $p < 0.05$, repeated-measures ANOVA; see amplitudes in Table 1). The post-hoc analysis showed that the responses to *Neutral* faces were $24 \pm 7\%$ stronger than the responses to *Provoked* or *Chronic* pain faces (*Provoked* vs. *Neutral* $p < 0.05$ and *Chronic* vs. *Neutral* $p < 0.05$, paired-samples t-tests).

In the right temporo-occipital area, all intact face stimuli (*Provoked* pain, *Chronic* pain, and *Neutral* faces) elicited strong, transient responses at 140–160 ms whereas the responses to *Scrambled* faces did not (Fig. 3b). The statistical tests confirmed the difference: the stimulus category showed a significant main effect (stimulus \times session; stimulus $p < 0.001$; see Table 1). The right-hemisphere responses to intact faces were on average $70 \pm 22\%$ (mean \pm SEM) stronger than the responses to scrambled images in the first measurement session (*Scrambled* vs. *Chronic* pain, $p < 0.05$; *Scrambled* vs. *Provoked* pain, $p < 0.01$, *Scrambled* vs. *Neutral*, $p < 0.05$; paired-samples t-tests). Similar stimulus effect was observed also for left temporo-occipital area at 140–170 ms (stimulus \times session; stimulus $p < 0.001$), and post-hoc tests confirmed the difference to originate from *Scrambled* vs. intact faces (*Scrambled* vs. *Chronic*, $p < 0.01$; *Scrambled* vs. *Provoked*, $p < 0.05$, *Scrambled* vs. *Neutral*, $p < 0.01$). No statistically significant differences were observed between any intact face categories (*Provoked*, *Chronic*, or *Neutral* face stimuli).

Effects of stimulus, hemisphere and session on activity in temporal lobes

The strongest temporal-lobe responses were elicited by *Provoked* pain faces. The three stimulus categories containing intact faces (*Chronic* pain, *Provoked* pain and *Neutral* faces) produced long-lasting, sustained responses peaking at 300–500 ms over the temporal lobes of both hemispheres, although stronger on the right (Fig. 3d,e). Fig. 4 shows the areal mean responses of all 9 subjects in the right hemisphere during the first measurement session, and the left top panel shows the across-subjects mean response. In 6 out of 9 subjects, the responses were clearly stronger for *Provoked* pain (red curves) than for any other stimulus category.

- Fig. 4 here -

In the statistical analysis (repeated-measures ANOVA) of these temporal-lobe responses, significant main effects were found for stimulus, session and hemisphere (stimulus \times session \times hemisphere; $p < 0.0001$, $p < 0.001$, $p < 0.005$, respectively; see Fig. 5 and Table 1 for details of response amplitudes). The strongest hemispheric difference appeared for the *Provoked* pain faces in the first measurement session: the sensor-level responses in the right hemisphere were about 40% stronger than in the left (amplitudes in the right and left hemisphere were 44 ± 3 fT/cm and 29 ± 3 fT/cm, respectively). An interaction effect was also found between stimuli and hemisphere (stimulus \times hemisphere, $p < 0.01$), indicating that the two hemispheres reacted differentially to the stimulus categories. Post-hoc tests revealed that the right hemisphere responses were $30 \pm 7\%$ stronger for *Provoked* pain than *Chronic* pain

faces ($p < 0.005$; see Fig. 4 and Table 1). Instead, the right-hemisphere responses for *Chronic* pain vs. *Neutral* faces did not differ ($p = 0.4$, n.s.).

Furthermore, the right-hemisphere responses for *Provoked* pain decreased by $24 \pm 4\%$ in the second session compared with the first ($p < 0.001$; mean responses 44 ± 3 fT/cm in the first and 33 ± 2 fT/cm in the second session; see Fig. 5). No similar modulations were found for *Chronic* pain faces in the right hemisphere.

– Table 1 here –

– Fig. 5 here –

Cortical sources of temporal-lobe responses

Fig. 6 shows the statistical maps of the current estimates for the 400 ± 50 ms time window for the whole cortex; the panels display both group-mean data (top row) and the data for 8 individuals for *Provoked* and *Chronic* pain faces, in both left and right hemisphere. These estimates suggest that the temporal-lobe responses for *Provoked* pain faces arose from the right, middle STS region (Fig. 6, second column from right); no signals were systematically observed in the homologue area in the left hemisphere at the same threshold. For *Chronic* pain faces, some weak activity was observed in the right hemisphere and no activity in the left.

– Fig. 6 here –

For the more detailed statistical analysis, the z-score values of the temporally-smoothed 300–500 ms responses and their peak latencies were collected from the ROIs of the right and left STS (Fig. 6; see also details in Table 2). Small main effects

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were found for both stimuli and hemispheres (stimulus \times hemisphere; $p < 0.01$ for stimulus and $p < 0.05$ for hemisphere, repeated-measures ANOVA). Responses to *Provoked* pain were $19 \pm 9\%$ stronger than responses to *Chronic* pain in the right STS area ($p < 0.05$, paired-samples t-test; see Table 2). Similarly, responses to *Provoked* and *Chronic* pain were $68 \pm 14\%$ and $39 \pm 10\%$ stronger in the right than left hemisphere, respectively ($p < 0.005$ and $p < 0.01$).

– Table 2 here –

Discussion

Early visual responses

As expected, all intact faces elicited significantly stronger responses than *Scrambled* faces at 140–160/170 ms in the temporo-occipital area. However, we found no systematic differences at this latency between responses to the *Provoked* pain, *Chronic* pain or *Neutral* faces, although some studies have suggested enhanced electric N170 responses for fearful faces [Batty and Taylor, 2003] or enhanced responses in the fusiform cortex to facial emotion expressions [e.g. Breiter et al., 1996; Ganel et al., 2005; Morris et al., 1998; Vuilleumier et al., 2001]. However, the temporo-occipital brain regions continue to process information at longer latencies, thus the fMRI results could reflect these later processes [e.g. Allison et al., 1999; Furey et al., 2006].

Single-cell recordings of human medial frontal cortex during brain surgery have indicated responses to facial expression of fear already at 120 ms [Kawasaki et al., 2001]. Moreover, a similar emotion-sensitive response, specifically to an

expression of fear, appears around 120 ms both at posterior and fronto-central EEG scalp electrodes [Eimer and Holmes, 2002; Eimer and Holmes, 2007; Pourtois et al., 2005]. Early responses to sad and happy facial expressions have also been associated to activation of the dorsal medial frontal cortex [Seitz et al., 2008].

In our study, the mid-occipital responses at 100 ms were stronger for *Neutral* faces than for *Chronic* or *Provoked* pain faces. Although these responses can be modulated by low-level attributes such as luminance and spatial frequency, the mean luminance of all stimulus categories in this study was equal, and systematic differences in spatial frequency were unlikely. However, *Neutral* and *Provoked/Chronic* pain faces differed on their contrast (as is evident from Fig. 1.), which can explain why the 100-ms mid-occipital responses were strongest to the *Neutral* faces [see e.g. Gardner et al., 2005; Tanskanen et al., 2005]. Moreover, since the *Neutral* faces depicted different persons than the pain faces, we will not discuss the differences in the mid-occipital responses further. Importantly, the higher visual areas are less sensitive to contrast [Avidan et al., 2002], and the main effects between the *Chronic* and *Provoked* pain stimuli were found at locations and latencies that are not sensitive to low-level attributes [Rolls, 2007; Rolls et al., 1987; Wallis and Rolls, 1997].

Modulation of STS responses by the intensity of pain expression and stimulus repetition

Here, we demonstrated that the middle STS responds more strongly to facial expressions of *Provoked* than *Chronic* pain; the main responses peaked at 300–500 ms with right-hemisphere dominance. Given the rather long latency of these STS responses, the observed modulation most likely reflects influences from other brain

regions. Previously, middle STS has been shown to respond to observed lip reading [Calvert et al., 1997], yawning [Schürmann et al., 2005], lip forms [Nishitani and Hari, 2002], and hand actions [e.g. Grezes et al., 1999; Nishitani and Hari, 2000; Rizzolatti et al., 1996]. Also single-cell recordings in monkeys [Hasselmo et al., 1989] and humans [Ojemann et al., 1992] have revealed STS neuronal populations responsive specifically for facial expression.

Nearby regions in the human STS are activated by other social stimuli. For example, the posterior STS responds to visual and auditory biological motion, e.g. to body movement observed from either point-light walkers [Bonda et al., 1996; Grossman et al., 2000], walking mannequins [Thompson et al., 2005], or animated walking humans [Pelphrey et al., 2003]. This area is also activated when the subject is listening to sounds of footsteps [Bidet-Caulet et al., 2005; Saarela and Hari, 2008]. Instead, the rostrally adjacent area along the sulcus reacts to eye gaze and mouth opening [Hoffman and Haxby, 2000; Puce et al., 1998; Wicker et al., 1998].

In fMRI recordings, a bilateral STS response has been associated with observation of video clips of acted pain [Simon et al., 2006] but not with observation of static pain expressions of true pain patients [Botvinick et al., 2005; Saarela et al., 2007]. This difference in STS reactivity might reflect sensitivity of the middle STS to mouth movements, which were visible in the video clips [Simon et al., 2006] but not in still images [Botvinick et al., 2005; Saarela et al., 2007]. Accordingly, the STS response profile during observation of static pain expressions might be better captured with time-sensitive electrophysiological methods than with the sluggish haemodynamic measures. In fact, here we showed that the STS responses for still photos of pain expressions decrease quickly, whereas a changing (e.g. moving) stimulus may elicit more sustained STS responses [Simon et al., 2006]. This

interpretation is in line with the recently proposed role of STS in analyzing temporally-varying visual and auditory stimuli for their communicative value [Redcay, 2008].

In our experiment, the right-hemisphere STS responses for *Provoked* pain expressions decreased from the first to the second session by a quarter, whereas no dampening was observed for *Chronic* pain faces. This decrease of the responses is in accordance with the long recovery cycle of cortical responses to real physical pain [Raij et al., 2003], compared with e.g. responses for innocuous touch in the primary somatosensory cortex [Hari and Forss, 1999] or responses to visual stimuli in the occipital cortices [Uusitalo et al., 1996]. Similarly, the *Provoked* pain expressions were rated as less intense after repeated exposure. This decrease of both subjective pain ratings and the strength of brain responses after several exposures to *Provoked* pain expressions agrees with the finding that healthcare professionals, who are repeatedly exposed to strong expressions of pain by strangers, attribute less pain to facial expressions of pain than do non-professionals [Kappesser and Williams, 2002]. Generally, the decrease of brain responses to repeated exposure for others' intense facial expressions could diminish the evoked affective load and thereby save the observer's resources; this view is supported by a recent finding that MEG responses to fearful faces at 300 ms also decrease from the first to the second presentation [Morel et al., 2009].

Similarities between brain correlates for facial expressions of pain and emotion

Emotionally salient stimuli have been proposed to capture attention reflexively due to their natural value for survival [Schupp et al., 2003], and the STS responses in

our study could have been affected by similar attentional processes—especially since attention to facially expressed emotion is known to enhance the fMRI response from the right STS [Narumoto et al., 2001; Pessoa et al., 2002; Winston et al., 2003].

The basic facial expressions of emotion do not include pain [Ekman et al., 1969] and the pain expression has been recently found to be more arousing and unpleasant than the emotion expressions [Simon et al., 2008]. Even so, the expression of pain has also much in common with emotions. For example, the experience of pain connects to a distinct facial expression, which communicates the internal state of the subject and is recognizable in most conspecifics [Prkachin et al., 2004; Williams, 2002]. Pain is also a highly affective experience in the same way as the emotions are. **Moreover, according to our results, the expression of pain observed from another’s face is processed at similar latencies and in similar cortical regions than has previously been reported for the facial expressions of emotions.**

The middle STS, here found to respond most strongly for *Provoked* pain faces, also responds to all basic emotional facial expressions with a right-hemisphere dominance [e.g. Engell and Haxby, 2007; Furl et al., 2007; e.g. Phillips et al., 1997; Winston et al., 2004; Vuilleumier et al., 2003]. Additionally, evoked scalp potentials have been observed at similar latencies around 300 ms for faces expressing happiness, surprise, fear and disgust [Ashley et al., 2004; Carretie and Iglesias, 1995; Krolak-Salmon et al., 2001]. In one of these studies [Krolak-Salmon et al., 2001], the responses were similar for all emotions at 250–550 ms, but differed at 550–750 ms.

The middle STS responses for *Provoked* pain faces in our study were strongly right-hemisphere dominant, suggesting hemispheric differentiation in processing of pain faces. Previously, right-hemisphere dominance has been observed during self-

experienced pain [e.g. Hari et al., 1997; e.g. Hsieh et al., 1996; Ostrowsky et al., 2002; Symonds et al., 2006]. Right and left hemispheres have also been suggested to have different effects on processing of the valence of emotions [for a review, see Killgore and Yrgelun-Todd, 2007]. Specifically, the right hemisphere has been suggested to allocate attention to the pain experience [Hsieh et al., 1996] and to have an important role in urgent and threatening situations [e.g. Adolphs et al., 1996; e.g. Davidson, 1992; Van Strien and Morpurgo, 1992]. The right-hemisphere dominance has been more often associated with negative emotional facial expressions, such as fear [Krolak-Salmon et al., 2001], and the facial expression of pain seems to communicate similarly urgent situation of a conspecific as does the fear expression. In addition, facial pain expressions are perceived as more arousing and unpleasant than any emotional faces of similar intensity [Simon et al., 2008].

Differences between neuromagnetic and haemodynamic responses for pain expressions

The transfer of an affective experience of pain from one person to another has been hitherto studied mainly by means of fMRI measurements, where visual or other cues of conspecific's pain have activated the ACC and AI regions in the observer's brain, closely resembling the activation during self-experienced pain. Thus, understanding others' pain experience seems to rely on similar experiences of the observer [for a review, see Hein and Singer, 2008]. Unfortunately, not much is yet known about the time course of brain responses to others' pain, since the haemodynamic measures have poor temporal acuity.

In our previous fMRI study, ACC and AI were more strongly activated during observation of *Provoked* than *Chronic* pain faces [Saarela et al., 2007] whereas no

such difference was seen in the present study. Besides differences between the fMRI and MEG methods, slightly different tasks were given to the subjects in these two studies, which could explain a part of the differences—the face-sensitive cortical processes after 200 ms are known to be modulated by the subject’s task [Furey et al., 2006; Lueschow et al., 2004]. In our fMRI study, the subjects were instructed to view all stimuli attentively to be able to answer questions of the stimuli afterwards, whereas here, we merely instructed the subjects to view all stimuli attentively but did not ask them to memorize any aspect of the stimuli.

An even more important reason for the differences between the previous fMRI study and the current MEG study is that ACC and AI are very difficult to detect in MEG recordings since (1) both sources are deep (leading to suppression of the MEG signal with respect to a more superficial source of equal strength), (2) ACC is symmetric (leading to signal cancellation because of opposite currents in nearby cortical walls), and (3) some currents in the insula are radial with respect to the skull surface and thus poorly visible in MEG [Hämäläinen et al., 1993]. For example, when the same laser-heat pain stimulus was used in both fMRI and MEG settings, the AI activation was evident in the fMRI measurements [Raij et al., 2005] but the MEG responses of the lateral cortex were adequately explained by activation of the second somatosensory cortex [Forss et al., 2005]. Indeed, according to our simulation using the anatomy of one subject, the source current in anterior insula has to be 3–4 times stronger than that in STS to produce an MEG response of the same magnitude.

Concluding remarks

In line with our hypothesis that viewing *Provoked* pain faces would recruit brain areas related to processing of observed emotional faces or affective pain, we

found that responses in the middle STS, peaking at 300–500 ms after stimulus onset, were stronger for *Provoked* than *Chronic* pain faces. These results resemble previous findings on facial expression of emotion in latency and, to some extent, location. In addition, the decrease of the responses for *Provoked* pain expressions from the first to the second measurement session could reflect an ecologically valid mechanism that protects the observer against a prolonged affective load.

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Figure legends

Fig. 1.

Examples of stimuli used in the experiment superimposed on mean-intensity gray background. The photos of the pain patients in their *Provoked* pain and *Chronic* pain conditions (during pain intensification and at rest, respectively) are shown in the box on the left, and the *Neutral* and *Scrambled* faces used for detecting general face-sensitive responses are shown on the right.

Fig. 2.

The 7-mm grid of source points at the border of grey and white matter is shown with pink triangles in coronal, axial, and sagittal brain sections of one subject. The grid covered the neocortex of both hemispheres.

Fig. 3.

Sample responses of a typical subject and the channel layout of the vector sums calculated from the gradiometers, seen from above. On left, the selections show the six channels of each area, from which the areal averages were calculated on the basis of the maximum responses: a) occipital cortex, b) right temporo-occipital cortex, c) left temporo-occipital cortex, d) right temporal lobe, e) left temporal lobe. On right, the representative responses of single channels, encircled in the whole-scalp view, have been magnified. The traces are from –200 ms to 1000 ms, and the amplitudes are given as fT/cm. The latencies of the peak amplitudes are marked on the single channel responses. Red = *Provoked* pain face, Black = *Chronic* pain face, Blue = *Neutral* face, Green = *Scrambled* face.

Fig. 4.

Grand average (MEAN) and individual areal average responses (S1–S9) of the right temporal lobe during the first session. Red = *Provoked* pain face, Black = *Chronic* pain face, Blue = *Neutral* face, Green = *Scrambled* face. The shadowed area indicates the 300–500 ms time window used for response quantification.

Fig. 5.

Signal strengths (mean \pm SEM) of temporal-lobe responses to different stimuli categories at 300–500 ms. Left: first measurement session. Right: second measurement session.

Fig. 6.

Estimates of the sources of the 300–500 ms activity in the whole cortex. The average (MEAN) across all subjects is overlaid on the atlas brain, and the current estimates of subjects S1–S8 are shown on their individual brain surface maps. Estimates for *Provoked* and *Chronic* pain faces of the first measurement session are shown separately in the left and right hemisphere. For visualization purposes, the color scales are individually normalized with respect to the individual signal-to-noise ratio.

In the grand average current estimates (MEAN) in the topmost panel, white ovals represent the ROIs for numerical statistical comparisons of the z-score amplitudes for *Provoked* and *Chronic* pain conditions.

**Table 1. The amplitudes of the responses at five sensor locations:
occipital cortex, bilateral temporo-occipital and temporal regions.**

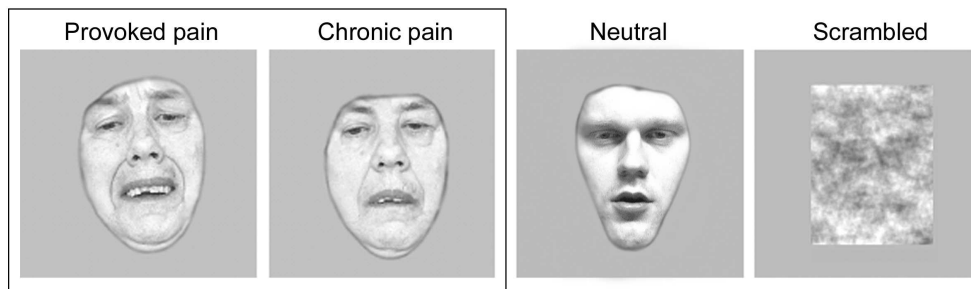
Location and Time window	SESSION 1				SESSION 2			
	Chronic	Provoked	Neutral	Scrambled	Chronic	Provoked	Neutral	Scrambled
Occipital 90–120 ms	56 (9)	53 (9)	66 (10)	51 (8)	55 (9)	52 (9)	64 (8)	53 (7)
Right temp-occ 140–160 ms	51 (7)	54 (7)	58 (7)	31 (2)	51 (8)	55 (7)	47 (7)	32 (3)
Left temp-occ 140–170 ms	51 (8)	49 (8)	45 (7)	38 (6)	45 (8)	48 (10)	42 (8)	37 (5)
Right temporal 300–500 ms	35 (3)	44 (3)	33 (3)	30 (2)	31 (3)	33 (2)	29 (3)	27 (1)
Left temporal 300–500 ms	26 (2)	29 (3)	23 (2)	24 (3)	24 (2)	23 (2)	19 (2)	23 (2)

The mean (SEM) amplitudes across all 9 subjects are given in femtoteslas per centimeter (fT/cm) for each stimulus condition, the two measurement sessions, and the left and right hemisphere (when applicable) at a given time window and sensor location.

Table 2. The individual z-scores and peak latencies of the left and right-hemisphere ROIs.

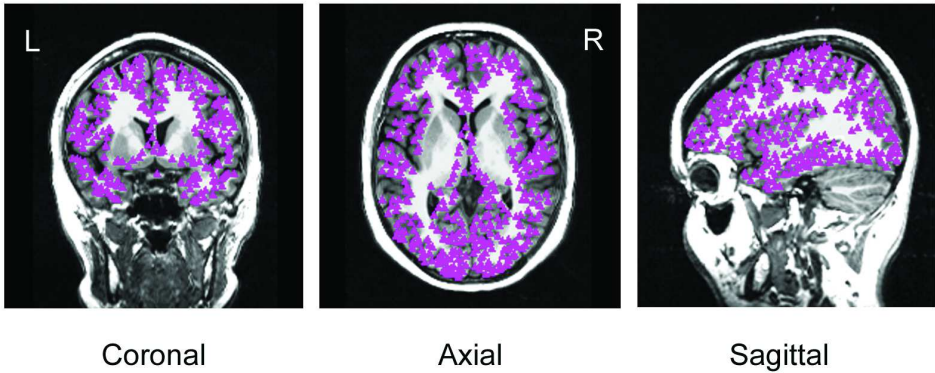
Subject	Left Hemisphere				Right Hemisphere			
	Chronic		Provoked		Chronic		Provoked	
	Z-score	Latency	Z-score	Latency	Z-score	Latency	Z-score	Latency
1	6.77	303	6.81	300	12.64	327	15.27	332
2	5.93	418	6.78	486	6.45	405	9.34	398
3	6.63	347	4.84	317	6.52	317	10.38	425
4	6.14	400	7.33	355	8.98	450	10.98	428
5	5.38	451	4.55	484	7.53	479	6.25	439
6	4.97	308	3.86	342	7.65	400	7.70	383
7	6.98	372	6.69	347	9.10	415	9.36	370
8	3.81	356	4.78	321	5.46	389	6.58	403

Response strengths of individual subjects in the ROIs of left and right hemispheres are the z-score values from the dynamical statistical parametric maps. The latencies are given in milliseconds.

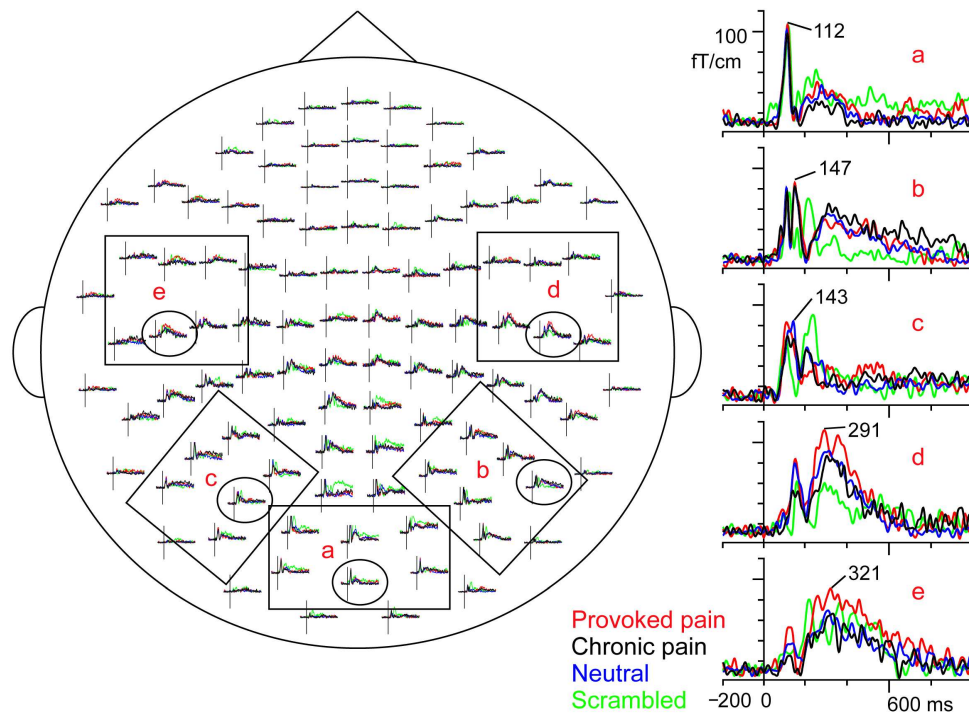


Examples of stimuli used in the experiment superimposed on mean-intensity gray background. The photos of the pain patients in their *Provoked* pain and *Chronic* pain conditions (during pain intensification and at rest, respectively) are shown in the box on the left, and the *Neutral* and *Scrambled* faces used for detecting general face-sensitive responses are shown on the right.

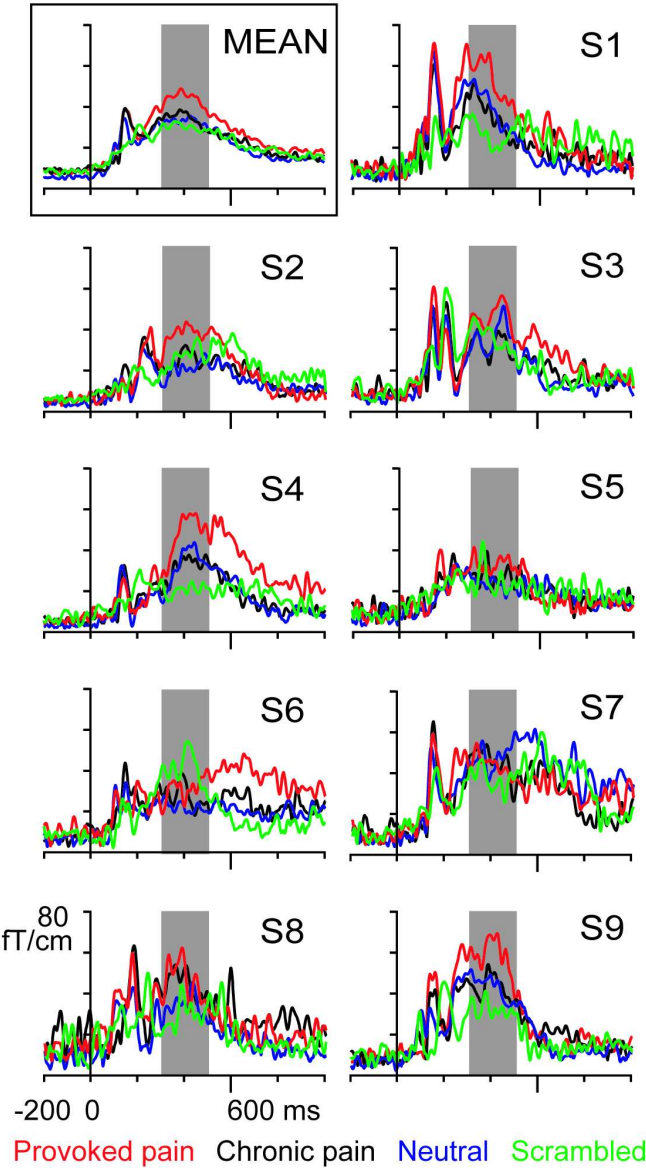
175x55mm (350 x 350 DPI)



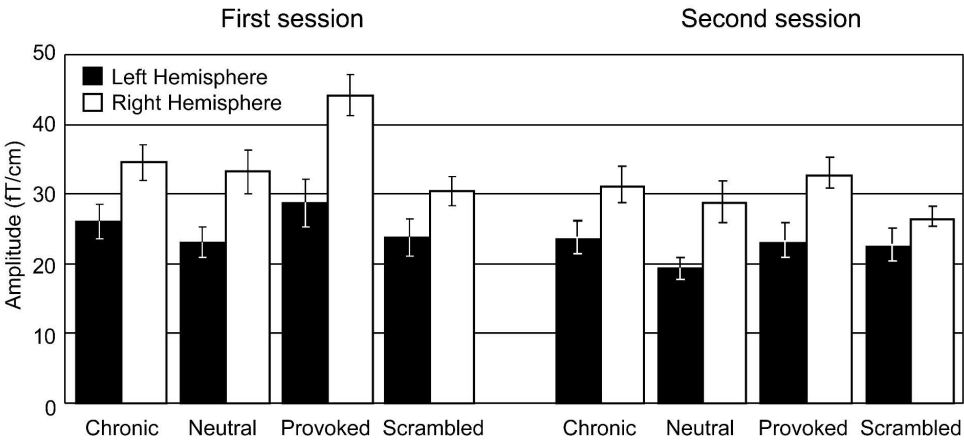
The 7-mm grid of source points at the border of grey and white matter is shown with pink triangles in coronal, axial, and sagittal brain sections of one subject. The grid covered the neocortex of both hemispheres.
142x60mm (300 x 300 DPI)



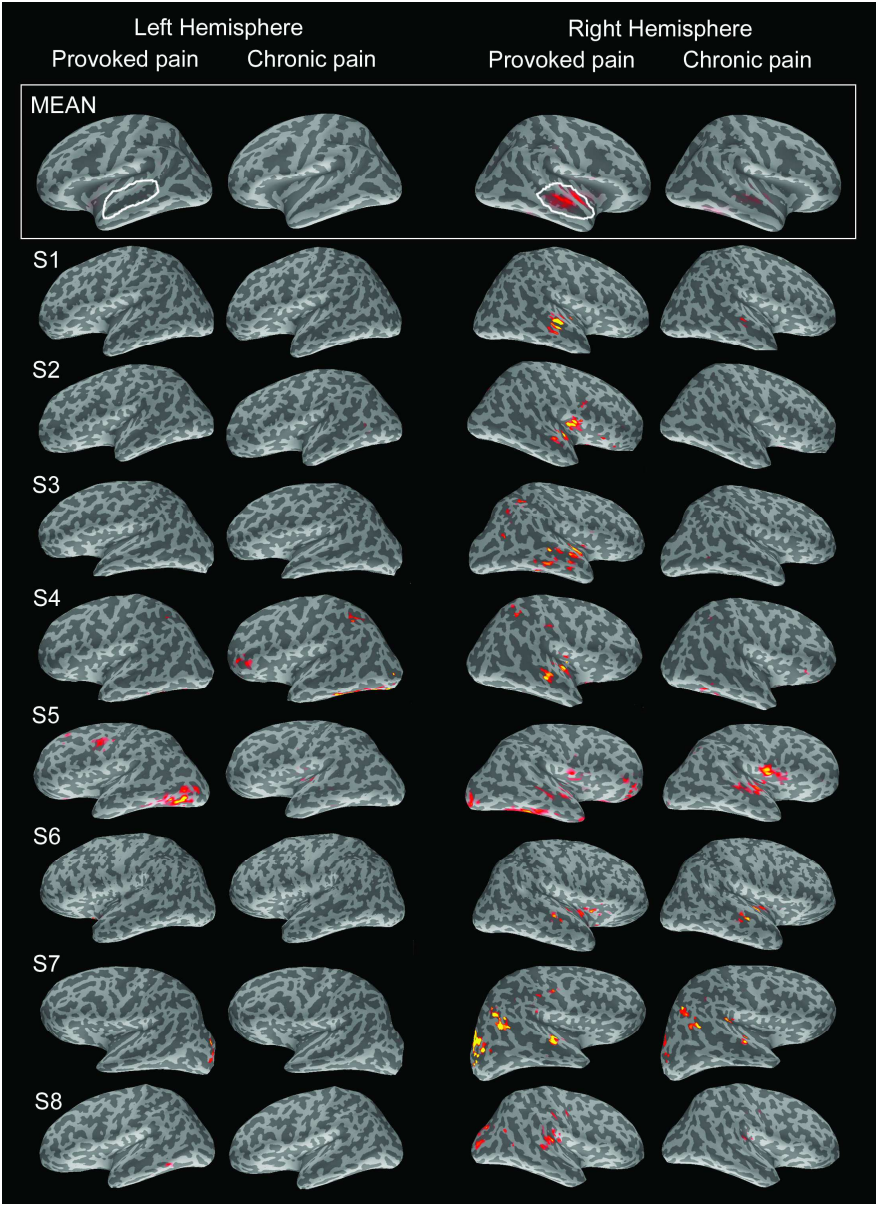
Sample responses of a typical subject and the channel layout of the vector sums calculated from the gradiometers, seen from above. On left, the selections show the six channels of each area, from which the areal averages were calculated on the basis of the maximum responses: a) occipital cortex, b) right temporo-occipital cortex, c) left temporo-occipital cortex, d) right temporal lobe, e) left temporal lobe. On right, the representative responses of single channels, encircled in the whole-scalp view, have been magnified. The traces are from -200 ms to 1000 ms, and the amplitudes are given as fT/cm. The latencies of the peak amplitudes are marked on the single channel responses. Red = *Provoked pain* face, Black = *Chronic pain* face, Blue = *Neutral* face, Green = *Scrambled* face. 174x133mm (350 x 350 DPI)



Grand average (MEAN) and individual areal average responses (S1-S9) of the right temporal lobe during the first session. Red = *Provoked pain* face, Black = *Chronic pain* face, Blue = *Neutral* face, Green = *Scrambled* face. The shadowed area indicates the 300-500 ms time window used for response quantification.
84x148mm (350 x 350 DPI)



Signal strengths (mean \pm SEM) of temporal-lobe responses to different stimuli categories at 300-500 ms. Left: first measurement session. Right: second measurement session.
165x80mm (600 x 600 DPI)



Estimates of the sources of the 300-500 ms activity in the whole cortex. The average (MEAN) across all subjects is overlaid on the atlas brain, and the current estimates of subjects S1-S8 are shown on their individual brain surface maps. Estimates for *Provoked* and *Chronic* pain faces of the first measurement session are shown separately in the left and right hemisphere. For visualization purposes, the color scales are individually normalized with respect to the individual signal-to-noise ratio.

In the grand average current estimates (MEAN) in the topmost panel, white ovals represent the ROIs for numerical statistical comparisons of the z-score amplitudes for *Provoked* and *Chronic* pain conditions.

160x219mm (350 x 350 DPI)

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