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Anticipatory cortical responses during the expectancy of a predictable painful stimulation. A high-resolution electroencephalography study

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Abstract

In the present study, high-resolution electroencephalography techniques modelled the spatiotemporal pattern of human anticipatory cortical responses preceding expected galvanic painful stimuli (non-painful stimuli as a control). Do these responses reflect the activation of associative other than somatosensory systems? Anticipatory processes were probed by alpha oscillations (6–12 Hz) for the evaluation of thalamocortical channels and by negative event-related potentials for the evaluation of cortical excitability. Compared with the control condition, a progressive reduction of the alpha power was recognized over the primary somatosensory cortex from 2 s before the painful stimulation. In contrast, the anticipatory event-related potentials were negligible during the expectancy period. The results on the alpha power suggest that the expectancy of the painful stimulation specifically facilitated the somatosensory thalamocortical channel. Remarkably, the associative frontal-parietal areas were not involved, possibly due to the predictable and repetitive features of the painful stimulus. The present results also suggest that negative event-related potentials are modest preceding warned stimuli (even if painful) with a simple information content.

Introduction

Attentional processes modulate regional blood flow reflecting activation of nociceptive cortical areas not only during pain experience but also in an anticipatory phase (Bushnell *et al.*, 1999; Hsieh *et al.*, 1999; Ingvar, 1999; Treede *et al.*, 1999; Petrovic *et al.* 2000; Peyron *et al.* 2000; Chen, 2001; Hofbauer *et al.* 2001). The anticipation of pain influences the primary somatosensory area, which is mainly devoted to sensory discrimination (Porro *et al.*, 1998, 2002; Treede *et al.*, 1999; Schnitzler & Ploner, 2000; Petrovic *et al.* 2002). Other regions involved by mechanisms of pain anticipation are the midline cingulate areas, which are engaged in affective/cognitive aspects of pain experience and selection of proper viscero-sensorimotor responses (Rainville *et al.*, 1997; Porro *et al.*, 1998, 2002; Hsieh *et al.*, 1999; Ingvar, 1999; Ploghaus *et al.*, 1999; Treede *et al.*, 1999; Petrovic *et al.* 2000; Schnitzler & Ploner, 2000; Petrovic & Ingvar, 2002).

Anticipation of pain triggers top-down attentional processes enhancing neuronal firing and modulating synaptic activity, which is indirectly related to changes of regional cerebral blood flow (Hsieh *et al.*, 1999; Ploghaus *et al.*, 1999). In line with previous evidence on other sensory modalities (Ghatan *et al.*, 1995; Rees *et al.*, 1997; Chawla *et al.*, 1999; Carlsson *et al.* 2000; Logothetis *et al.* 2001; Porro *et al.* 2002), activity of the primary somatosensory cortex increases in a somatotopic fashion corresponding to the body region where the subject is waiting for the stimulus (Porro *et al.* 2002) and decreases in the adjacent cortical areas (Drevets *et al.*, 1995; Porro *et al.* 2002). Furthermore, anterior cingulate and medial orbitofrontal areas are up-regulated during the anticipation of an unlearned and unpredictable painful stimulus, possibly to recruit resources for the management of the incoming event (Hsieh *et al.*, 1999). However, the anticipation of predictable, repetitive and learned stimuli (i.e. carrying poor informational content) could not require an important involvement of associative frontal areas. Rather, these areas would be down-regulated in that condition possibly to distract sensory processing from the pain source (Hsieh *et al.*, 1999). Notably, this effect is inversely correlated with the degree of anxiety (Simpson *et al.* 2001).

Synaptic concomitants of anticipatory attentional processes can be roughly but directly indexed by two electroencephalography (EEG) parameters. The first index is based on the EEG oscillations at extended alpha band (6–12 Hz). The lower the amplitude of these oscillations the better the information transfer ('gating') through sensorimotor thalamocortical and cortico-cortical pathways (Klimesch, 1999; Pfurtscheller & Lopes da Silva, 1999). The second index is obtained by averaging the slow EEG oscillations across single

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trials in the period between warning and imperative go stimuli (Brunia, 1999; Brunia & van Boxtel, 2001). The averaging procedure produces slow negative event-related potentials (ERPs) or contingent negative variation, which denote affective-motivational cortical processes other than preparatory sensorimotor processes (Böcker *et al.* 2001; Böcker & van Boxtel, 1997). When no motor response is required, contingent negative variation is termed stimulus-preceding negativity (SPN; Brunia, 1999; Brunia & van Boxtel 2001). Both contingent negative variation and SPN reflect an anticipatory increment of the cortical excitability (Brunia, 1999).

As distinctive features of the above EEG indices, SPN has a negligible amplitude if the upcoming stimulus provides no feedback or instructions (Chwilla & Brunia, 1991; Kotani & Aihara, 1999; Brunia & van Boxtel 2001; Filipovic *et al.* 2001; Bastiaansen *et al.* 2002). Furthermore, low-band alpha EEG oscillations (6–10 Hz) are modulated by general attention as opposed to task-specific processes related to high-band alpha EEG oscillations (10–12 Hz; Klimesch *et al.*, 1996; Klimesch, 1996, 1997, 1999).

In the present study, high-resolution EEG techniques modelled the spatiotemporal pattern of human anticipatory cortical responses preceding expected galvanic painful stimuli (non-painful stimuli as a control). Do these responses reflect the activation of associative other than somatosensory systems? Anticipatory processes were probed by extended alpha oscillations (6–12 Hz) for the evaluation of thalamo-cortical channels and by negative ERPs for the evaluation of cortical excitability.

Materials and methods

Subjects

Fourteen young (age 25 ± 3.1 years) healthy volunteers participated in the present study. All subjects gave their written informed consent according to the Declaration of Helsinki and could freely request an interruption of the investigation at any time. The general procedures were approved by the local institutional ethics committee.

Stimulation procedure

Subjects were seated in a comfortable reclining armchair. Constant current monophasic pulses of 5 ms were applied intracutaneously to the tip of the left index finger. After drilling a hole in the stratum corneum, a specially constructed electrode was inserted and fixed on the skin (Bromm *et al.*, 1989). This electrode consisted of a gold pin (cathode) and a ring electrode (anode) placed in the first phalanx of the left index finger. A conductive bracelet (wrist) served as a ground.

The experimental design included two levels of predictable galvanic stimulation, i.e. non-painful and moderately painful. Non-painful and moderately painful stimuli were given in separate recording blocks and subjects were told the level of the simulation at the beginning of each recording block. Therefore, they could reliably predict the kind of galvanic stimulation (i.e. painful or non-painful) across that recording block. The magnitude of the stimulation was determined by a series of increasing and decreasing stimulus intensities at the beginning of each recording block. The procedure was as follows. During the setting of the stimulus intensity, subjects had to rate verbally the stimulus magnitude on a numerical scale ranging from 0 (no sensation) to 10 (pain tolerance threshold). On this scale, the subjective evaluation was 1 for sensory threshold, 2 for strong sensory (just below painful threshold), 3 for painful threshold, 4 for slight pain, 5 for intermediate pain, 6 for moderate pain and so on up to 10. For the present experiments, the galvanic stimulation was delivered at level 2 (strong sensory but not painful) in the non-painful recording blocks and at level 6 (moderate pain) in the painful recording blocks. At the end of each block subjects verbally reported no habituation effects to the electrical stimuli.

A trial of the experimental paradigm was as follows. Three visual stimuli were delivered by a personal computer in front of the subject (yellow target, 0.5 s duration). A galvanic stimulus was then given instead of a fourth visual stimulus. The interval between the onset of consecutive visual stimuli and between the onset of the third visual and galvanic stimuli was 4 s. The interval between the onsets of two consecutive galvanic stimuli was 16 s. A brief training session served to minimize blinking and eye movements (from 5 before to 1 s after galvanic stimulus).

Electroencephalography recordings

The EEG data were recorded (NeuroScan System, El Paso, Texas, USA; bandpass, 0.05–100 Hz, sampling rate, 250 Hz) from 62 electrodes placed according to an augmented 10–20 system. Linked-ears served as an electrical reference and the electrode impedance was kept lower than 5 kΩ. Two electro-oculographic channels were used to monitor eye movements and blinking. Furthermore, bipolar recordings of the electrocardiogram signals were obtained from two electrodes properly located to collect well-shaped R peaks.

The acquisition time for all data (EEG, electro-oculographic and electrocardiogram) was set from -14 to $+2$ s after the galvanic stimulation taken as zero time. About 50 EEG trials with NOPAIN task (± 2.7, SE) and 50 EEG trials with PAIN task (± 3.3, SE) were collected for each stimulus condition and for each subject. The selection of subjects and EEG recordings were performed at the University of Aalborg (Denmark) while the data analysis was performed at the University of Rome (Italy).

Measurement of heart rate deceleration

The index of the heart rate deceleration (HRD) was extracted for both non-painful and painful conditions. Computer-assisted procedures were developed to minimize the experimenter errors in the index extraction.

The HRD index was computed as follows. For each of the single trials, the R-R intervals were measured in the period between the second and third visual stimuli as a baseline measurement of the heart rate (baseline period). The R-R intervals were also measured in the period between the third visual stimulus and the galvanic stimulus as a measurement of heart rate during the expectancy of the galvanic stimulation (expectancy period).

Preliminary data analysis

The EEG single trials contaminated by blinking, eye movements and involuntary motor acts were rejected off-line. The spatial resolution of artifact-free EEG data was enhanced by surface Laplacian estimation (regularized three-dimensional spline function), which reduces low spatial frequencies of EEG distribution possibly due to head volume conductor effects (F. Babiloni *et al.*, 1996, 1998, 2001; Nunez, 1996). Furthermore, surface Laplacian estimation annuls electrode reference influence (Nunez, 1995).

The single trial analysis was carefully repeated on the Laplacian-transformed EEG data to discard the single trials contaminated by computational artifacts. On average, the mean of the individual artifact-free data was of 38 (± 4.2, SE) single trials for both tasks.

Computation of the event-related desynchronization/synchronization

For the EEG spectral analysis, the frequency bands of interest were alpha 1, alpha 2 and alpha 3. These frequencies were determined

according to a standard procedure based on the peak of individual alpha frequency (IAF; Klimesch, 1996, 1999; Klimesch *et al.*, 1998). With respect to the IAF, these frequency bands were defined as follows: (i) alpha 1, IAF − 4 Hz to IAF − 2 Hz, (ii) alpha 2, IAF − 2 Hz to IAF and (iii) alpha 3, IAF to IAF + 2 Hz. This power spectrum analysis was based on an FFT approach using the Welch technique and Hanning windowing function.

The event-related desynchronization/synchronization (ERD/ERS) of alpha EEG oscillations was obtained using:

$$\mathrm{ERD\%} = 100 \times (E - R)/R$$

where E indicates the power density at the 'event' (lasting 1000 ms) and R the power density at the 'baseline or rest' (lasting 1000 ms). For simplicity, we referred to the event-related percentage changes of alpha band power as ERD/ERS, which usually denotes percentage variations of EEG power for time samples of about 100 ms (Pfurtscheller *et al.*, 1997, 1999; Pfurtscheller & Lopes da Silva, 1999). The statistical significance ($P < 0.05$) of the individual ERD values was evaluated by the sign test according to standard guidelines (Pfurtscheller *et al.*, 1997, 1999; Pfurtscheller & Lopes da Silva, 1999). The ERD/ERS was computed for the IAF-based alpha 1, alpha 2 and alpha 3. The 'baseline' for the ERD/ERS computation was defined as the period of 1000 ms before the third visual stimulus. The 'events' were the periods from −2000 ms to −1000 ms ('EXP early') and from −1000 ms to the galvanic stimulation ('EXP late') taken as zero time. For the statistical analysis, we used the 1-s ERD period as the anticipatory process was characterized by a slow shift rather than by a transient phenomenon. The slow development of the anticipatory ERD was observed by an FFT-based time frequency analysis producing temporal curves of ERD at electrodes of interest.

For illustrative purposes, we performed a fine time–frequency analysis of EEG data during the expectancy of non-painful and painful galvanic stimulations. Spectral values time-by-time were obtained by computing power spectral density (PSD) by the averaged periodogram method (Hanning windowing, 1 s windows) every 100 ms from −6 s to zero time (stimulation). This yielded a frequency resolution of 1 Hz in the alpha and beta range. The results at electrodes of interest were illustrated by three-dimensional diagrams in which the x axis represented time (s), the y axis represented spectral frequency (Hz) and the z axis represented PSD (arbitrary units). A colour scale indicated the ERD/ERS values (%) computed with respect to PSD values relative to a baseline period occurring from −5 to −4 s.

Laplacian event-related potentials and somatosensory-evoked potentials

Artifact-free single trials were averaged with respect to the galvanic stimulus delivery (zero time) to generate Laplacian ERPs and somatosensory-evoked potentials. The baseline for the measurement of the amplitude of the Laplacian ERPs was taken during the period of 500 ms before the galvanic stimulus (the period of 500 ms before the third visual stimulus). The mean amplitude of the Laplacian ERPs was measured as follows: the vertex N2-P2 complex (amplitude difference between the two main negative and positive peaks) and P3 (amplitude of the P3 component). According to the 10–20 montage system, the electrodes of interest for these measurements overlaid the left (F3) and right (F4) dorsolateral prefrontal areas, cingulate areas (Fz, Cz and Pz) and primary sensorimotor areas contralateral (C4) and ipsilateral (C3) to the stimulation. Of note, the surface Laplacian estimation used the information of all 62 electrodes to spatially enhance the potentials at the electrode of interest (F. Babiloni *et al.*, 1996).

Topographic mapping

Topographic maps (256 hues) of the Laplacian ERPs were calculated on a three-dimensional 'quasi-realistic' head model by a spline interpolating function (F. Babiloni *et al.*, 1995, 1996). This model is based on the magnetic resonance data of 152 subjects digitized at the Brain Imaging Center of the Montreal Neurological Institute (SPM96, http://www.mni.mcgill.ca) and is commonly considered as an acceptable template for the rendering of group neuroimaging data.

Statistical analysis

Statistical comparisons were performed on Laplacian EEG data by ANOVA for repeated measures. Mauchley's test evaluated the sphericity assumption when necessary. Correction of the degrees of freedom was made by the Greenhouse–Geisser procedure when necessary and the Duncan test was used for post-hoc comparisons ($P < 0.05$).

Statistical analysis of the alpha ERD/ERS comprised the factors Condition (NOPAIN and PAIN), Band (alpha 1, alpha 2 and alpha 3), Electrodes of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Expectancy time period (EXP early and EXP late). The working hypothesis of a modulation of the alpha ERD would be corroborated by a statistical ANOVA interaction among Condition and the other factors.

A similar ANOVA design evaluated the anticipatory Laplacian ERPs. It comprised the factors Condition (NOPAIN and PAIN), Electrodes of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Expectancy time period (EXP early and EXP late). Again, the working hypothesis would be corroborated by a statistical ANOVA interaction among Condition and the other factors. In addition, an ANOVA design tested the global quality of the ERPs following the galvanic stimulations. It included the factors Condition (NOPAIN and PAIN), Electrode of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Time (N2, P2 and P3). A significant increase of the Laplacian ERPs was expected after the painful compared with non-painful galvanic stimulations.

Results

Heart rate deceleration

No statistical difference in HRD was found ($F_{1,11} = 2.05$; $P = 0.18$) between the two conditions (NOPAIN and PAIN), thus suggesting no significant autonomic difference as revealed by such a psychophysiological index.

Topography of spectral electroencephalography data

Power density spectra of Laplacian EEG data are shown in Fig. 1 (grand average). These spectra refer to the electrodes of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and to the two conditions (NOPAIN and PAIN). For the NOPAIN condition, the spectra were characterized by an alpha peak (about 10 Hz) stronger in power at Pz than at other electrodes. Compared with these spectra, the expectancy of the painful stimuli mainly induced a decrease of the alpha power at C4 and C3 electrodes. Maps of the alpha ERD/ERS fully confirmed these topographical results (Fig. 2).

Statistical analysis of alpha event-related desynchronization/synchronization

ANOVA analysis of the Laplacian alpha ERD/ERS pointed to a statistical interaction ($F_{8,104} = 2.05$; $\mathrm{MSe} = 892$; $P < 0.05$) among the factors Condition (NO PAIN and PAIN), Electrode of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Time (EXP early and EXP late). As a main result, post-hoc testing indicated that the alpha ERD at C3 ($P < 0.01$) and C4 ($P < 0.0001$) was stronger during the late

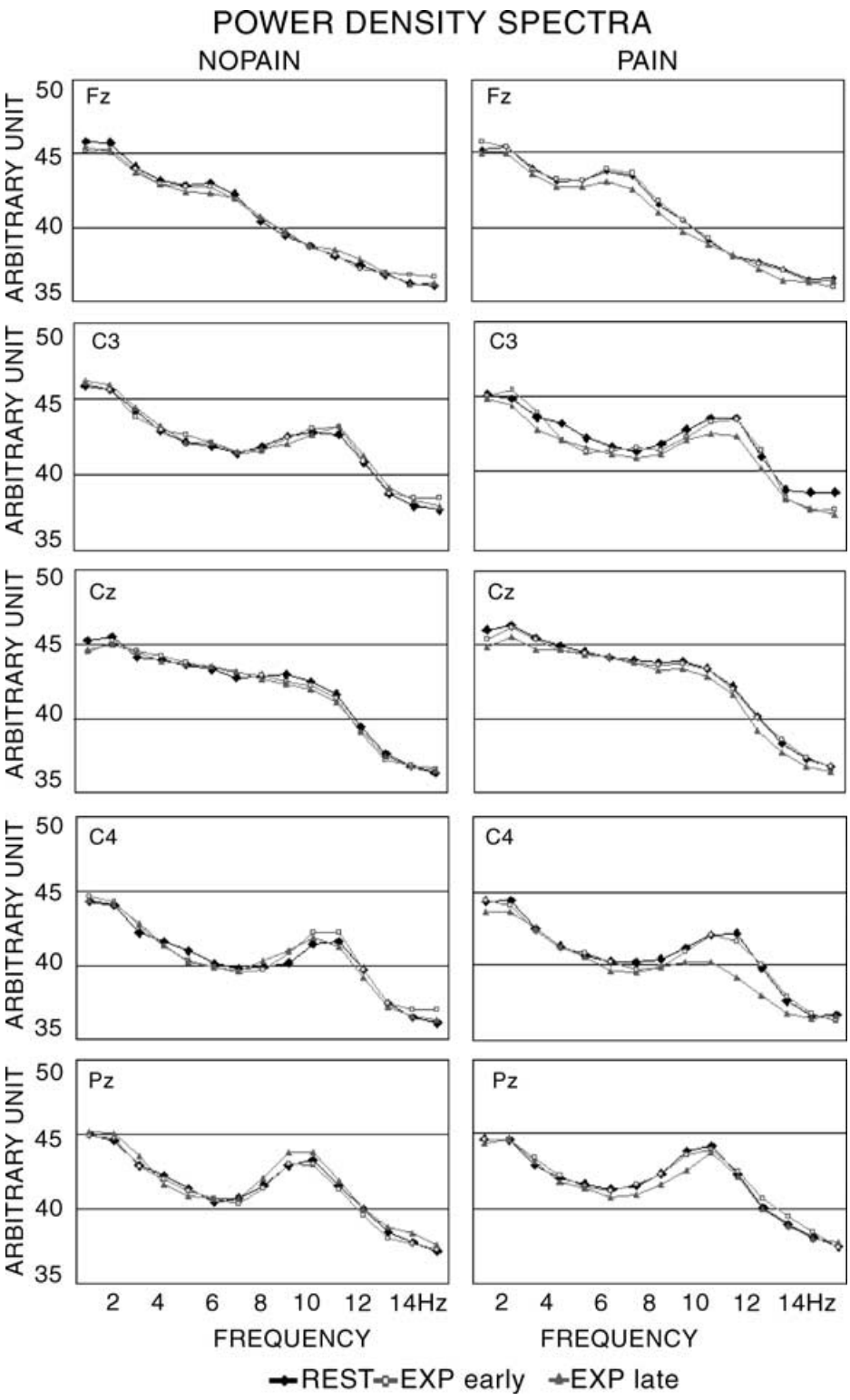

FIG. 1. Electroencephalography (EEG) power density spectra (grand average) at electrodes of interest (Fz, C3, Cz, C4 and Pz) for the two conditions (NOPAIN and PAIN). The spectra refer to the periods of baseline (1000 ms, REST), the early expectancy (from −2000 to −1000 ms, EXP early) and late expectancy (from −1000 ms to zero time, EXP late). The recorded EEG data were preliminary Laplacian transformed to minimize the effects of the head volume conduction and to annul the influence of the electrode reference.

expectancy of painful than non-painful stimuli (Fig. 3). Of note, a control ANOVA analysis demonstrated that this difference was not due to the alpha power at the baseline period. Figure 4 shows the evolution in time of mean PSD and ERD/ERS at the electrodes of interest in both NOPAIN and PAIN conditions. The PSD and ERD/ERS are represented as functions of both time (−6 s to zero time as the instant of electrical stimulation) and spectral frequency (5–25 Hz). In Fig. 4, the *x* axis represents time (s), the *y* axis represents spectral frequency (Hz)

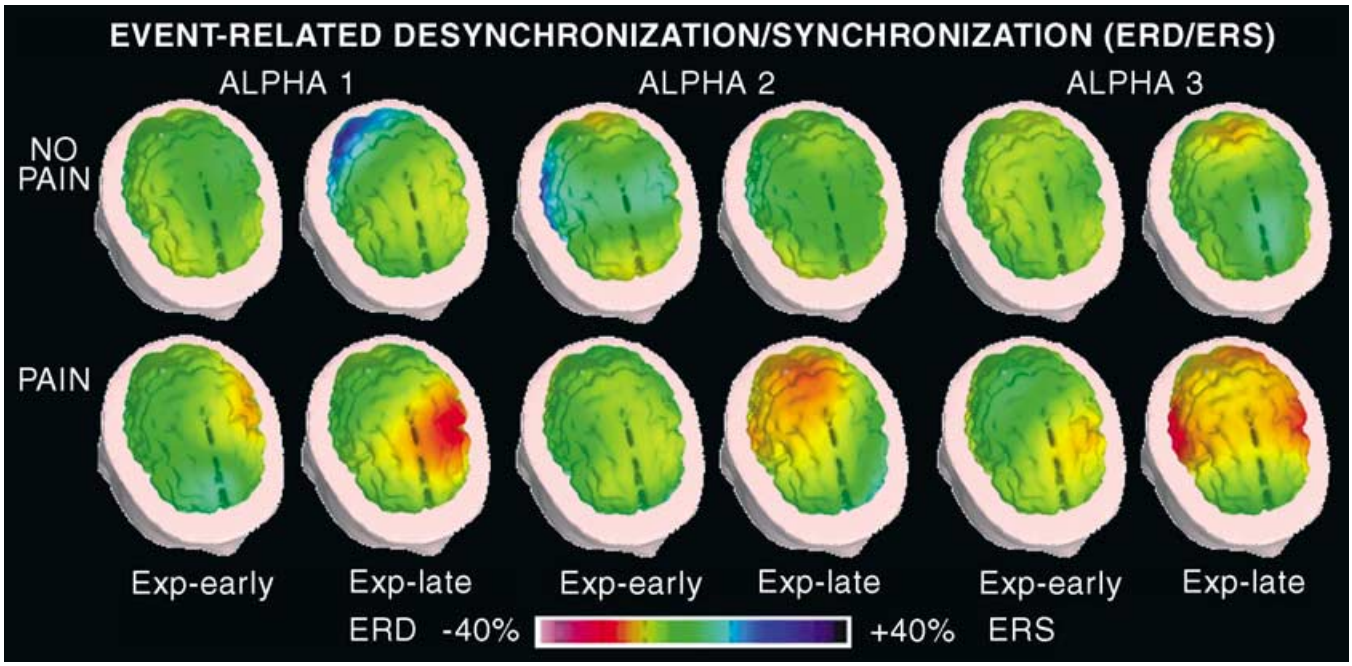

FIG. 2. Topographical maps of the event-related desynchronization/synchronization (ERD/ERS) for the three alpha sub-bands (alpha 1, alpha 2 and alpha 3). The ERD/ERS refers to both conditions (NOPAIN and PAIN) and both expectancy periods (EXP early and EXP late).

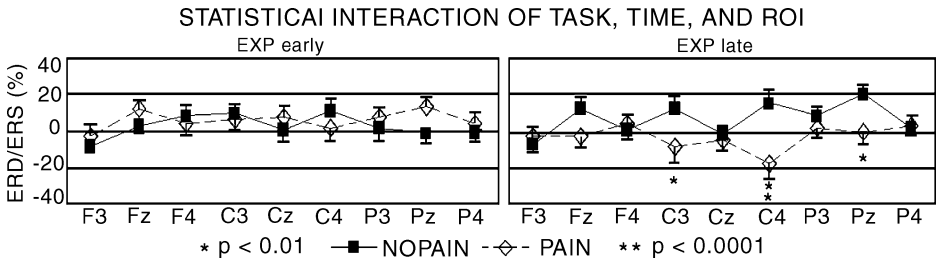

FIG. 3. Group means ±SE of the alpha event-related desynchronization/synchronization (ERD/ERS) as provided by the ANOVA analysis. In particular, these means refer to a statistical interaction among the factors Condition (NOPAIN and PAIN), Time (EXP early and EXP late) and Electrode of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4). The results of Duncan post-hoc testing are indicated by one ($P < 0.01$) or two ($P < 0.0001$) asterisks. ROI, region of interest.

and the z axis represents PSD (arbitrary units). Figure 4 shows slow changes in time of spectral profile during the expectancy period. The red colour code indicates that alpha ERD was evident at C3 and especially at C4 ($P < 0.0001$) during the late expectancy of painful but not non-painful stimuli. These results are fully in line with the above ANOVA solutions computed for 1-s early and late expectancy periods.

Spatio-temporal pattern of event-related potentials

During the expectancy of the non-painful or painful stimuli, negative ERPs (SPN) were observed in only three of 14 subjects. This prevented a statistical comparison of the negative ERPs preceding the galvanic stimulations. For illustrative purposes, the grand average waveforms of the Laplacian ERPs (all subjects) are illustrated in Fig. 5. The anticipatory ERPs were negligible. In contrast, the somatosensory-evoked potentials following non-painful and painful stimuli were well shaped. The N2-P2 and P3 components peaked at scalp vertex (Cz site) and were stronger in amplitude after the painful than non-painful stimulations.

Statistical analysis of event-related potentials

ANOVA analysis showed a statistical interaction ($F_{24,312} = 14.53$; MSe = 566; $P < 0.00001$) among the factors Condition (NOPAIN and PAIN), Electrode of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Time (N2, P2 and P3 components). Post-hoc testing confirmed the acceptable quality of the data as revealed by a greater amplitude of the potentials evoked by painful than non-painful stimulations at central electrodes ($P < 0.05$–0.01; Fig. 6).

Discussion

Methodological remarks

A special pin electrode served to stimulate predominantly A delta fibers belonging to the nociceptive system during the painful condition (Bromm *et al.*, 1989). The intracutaneous stimulation caused a sharp and well-localized painful sensation, very similar to the pain sensation induced by tooth pulp stimulation. This stimulation evoked brain responses recordable from the scalp as a vertex negative–positive complex (N2-P2), which was stronger in amplitude than that of non-painful stimulation (see also Bromm & Meier, 1984; Chen, 1993; Bromm & Lorenz, 1998; C. Babiloni *et al.* 2001, 2002). Of note, the involvement of tactile A beta fibers cannot be excluded after the present painful stimulation. However, it should be stressed that the level of the non-painful stimulation (eliciting strong sensory sensation) was set to recruit most of these fibers and to saturate their activity.

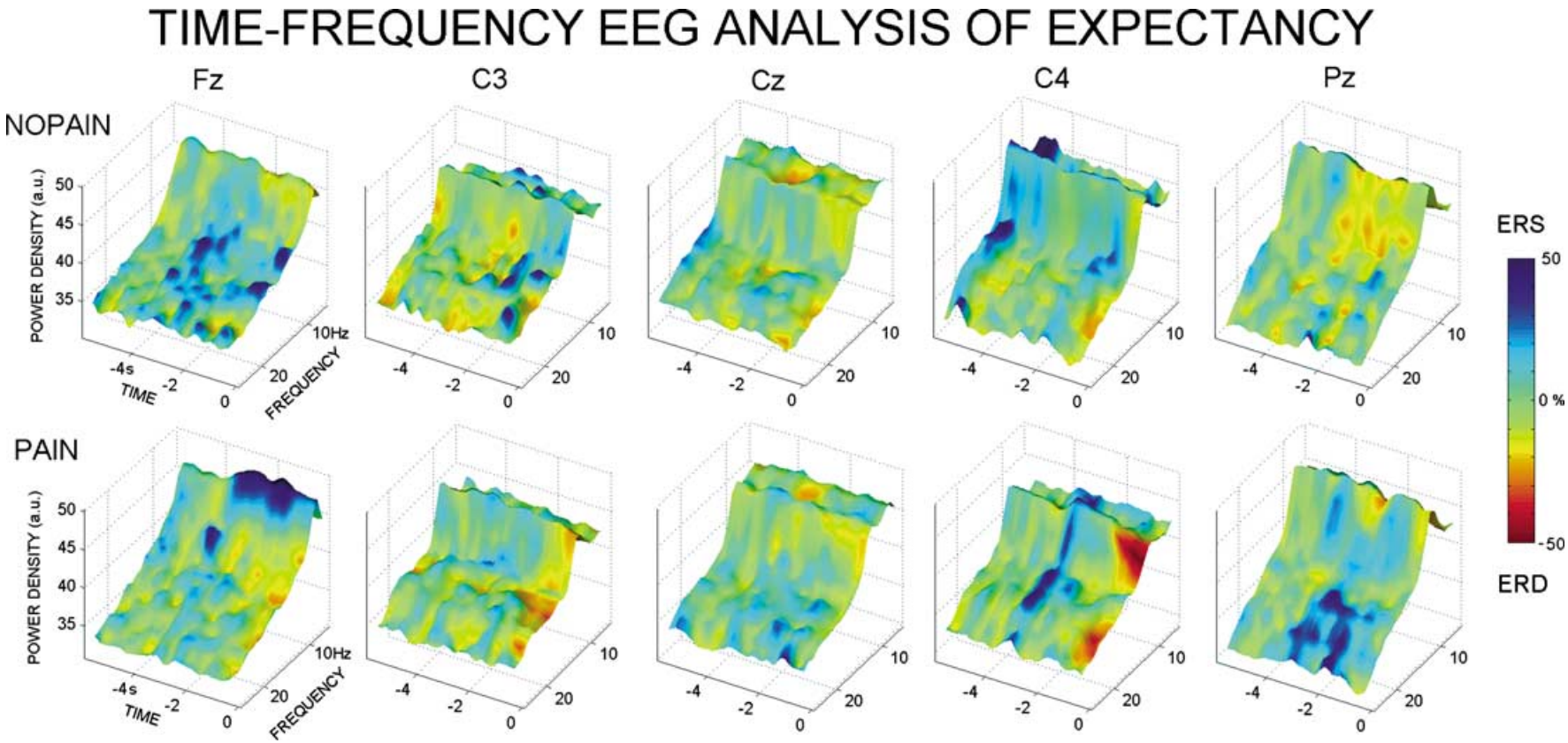

FIG. 4. Evolution in time of mean power spectral density (PSD) and event-related desynchronization/synchronization (ERD/ERS) at the electrodes of interest in both NOPAIN and PAIN conditions. The PSD and ERD/ERS are represented as functions of both time (−6 s to zero time as the instant of electrical stimulation) and spectral frequency (5–25 Hz). The *x* axis represents time (s), the *y* axis represents spectral frequency (Hz) and the *z* axis represents PSD (arbitrary units). Slow changes in time of spectral profile during the expectancy period are shown. The red colour code indicates that alpha ERD was evident at C3 and especially at C4 ($P < 0.0001$) during the late expectancy of painful (PAIN) but not non-painful (NOPAIN) stimuli.

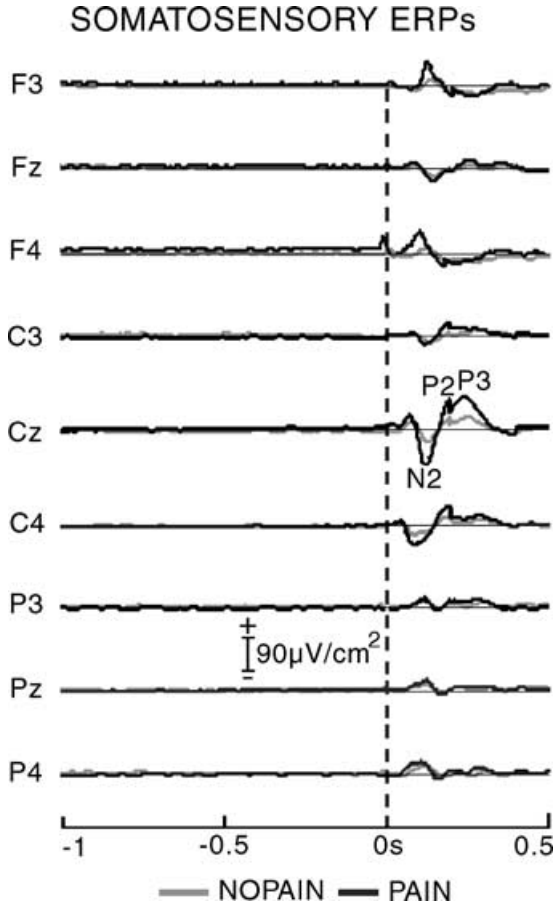

FIG. 5. Grand average waveforms ($n = 14$) of the Laplacian event-related potentials (ERPs) computed at electrodes of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) during and following the expectancy of the galvanic stimulations (NOPAIN and PAIN).

The spatial resolution of the surface Laplacian estimates should be considered with caution (F. Babiloni *et al.* 2001). Indeed, relevant cortical sources in secondary somatosensory and insula areas (Chen, 1993, 2001; Kitamura *et al.*, 1995; Chen *et al.*, 1998) could not be investigated, as the surface Laplacian estimate is not fully reliable when computed at the border temporo-parietal electrodes (Nunez, 1996). Furthermore, surface Laplacian maxima could not always overlie cortical sources of EEG potentials, due to the influence of tangential rather than radial generators (F. Babiloni *et al.*, 1995, 1996). However, it should remarked that the present EEG spatial sampling (62 electrodes) was higher than that of all previous field studies (Chen, 1993; Bromm & Lorenz, 1998; Chen *et al.*, 1998). Therefore, it was assumed that surface Laplacian estimates from such a high spatial sampling may provide a useful model of the neuroelectrical cortical activity.

Anticipation of pain enhanced somatosensory thalamocortical channel as revealed by alpha event-related desynchronization

In the present experiments, the alpha EEG oscillations decreased in power (ERD) over the primary somatosensory cortex. As a striking result, the decline of the alpha oscillations was stronger during the expectancy of painful than non-painful stimulations and was more evident over the contralateral than ipsilateral primary somatosensory cortex. The functional meaning of the alpha ERD (Klimesch *et al.*, 1996; Klimesch, 1996, 1997, 1999) and its localization over the primary somatosensory cortex point to an attentional and sensory-specific cortical preparation during the anticipation of pain.

These results extend previous reports in humans pointing to a large decrease of sensorimotor alpha activity during stimuli signalling relevant events (Klimesch *et al.*, 1998), during the planning of voluntary movements (Pfurtscheller & Lopes da Silva, 1999) and during the expectancy of informative stimuli (Bastiaansen & Brunia, 2001; Bastiaansen *et al.* 2001; Filipovic *et al.* 2001) or of painful stimulation (Rockstroh *et al.*, 1989, fig. 5.22). In this framework, thalamocortical information flow to the primary somatosensory cortex may be facilitated by thalamic reticular cells, according to a modern view of the generation of cortical alpha rhythms (Brunia, 1999). Future studies should investigate the correlation among the anticipatory alpha ERD over primary somatosensory cortex, the parameters indexing efficacy of pain perception (i.e. recognition and learning) and the concomitant viscero-motor regulation (Schnitzler & Ploner, 2000).

Anticipation of pain per se is not able to induce anticipatory event-related potentials (stimulus-preceding negativity)

During the anticipation of the painful stimulation, no HRD was found and the modulation of the negative ERPs (SPN) was observed in only three of 14 subjects. This is apparently at variance with previous neuroimaging evidence showing an activation of a complex neural network including frontal areas, such as anterior cingulate cortex and insular cortex, during the anticipation of painful stimulations as well as an activation of more caudal areas, such as posterior cingulate cortex,

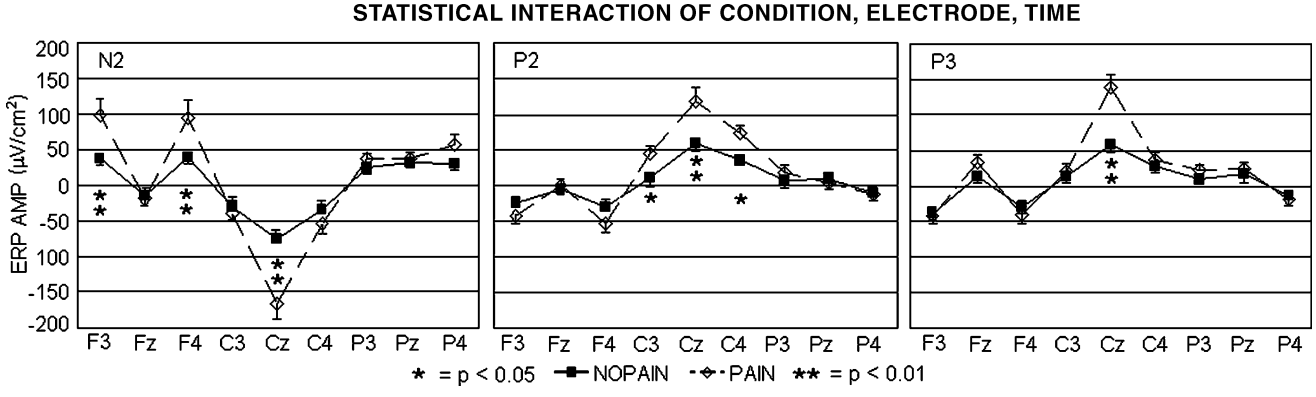

FIG. 6. Group means (± SE) of the Laplacian somatosensory-evoked potentials relative to a statistical interaction among the factors Condition (NOPAIN and PAIN), Electrode of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4) and Time (N2-P2 potential complex and P3 peak). The results of Duncan post-hoc testing are indicated by one ($P < 0.05$) or two ($P < 0.01$) asterisks. ERP, event-related potential.

during effective painful stimulation (Hsieh *et al.*, 1999; Ploghaus *et al.*, 1999; Porro *et al.* 2002). In the present study, the lack of frontal activation found may be due to the fact that the stimulation was repetitive, brief and highly predictable and that no subjective stimulus appraisal was requested trial-by-trial. Moreover, painful and non-painful stimuli were always of the same intensities and were delivered in separate blocks allowing the subject to predict the kind of stimulus received. This stimulation modality could have diminished the affective/emotional colouring of the upcoming stimulus and, hence, the activation of rostral areas of the cingulate cortex. On the contrary, previously quoted studies have employed prolonged painful stimulations with some temporal or modal uncertainty. In addition, subjects had to evaluate pain intensity trial-by-trial. It is reasonable that similar experimental conditions provoked a marked response of the anterior cingulate cortex, which is sensitive to tonic stimulations and situations enhancing affective resonance of pain stimulation (Hsieh *et al.*, 1999; Treede *et al.*, 1999; Schnitzler & Ploner, 2000; Vogt & Sikes, 2000; Porro *et al.* 2002). Remarkably, medial orbitofrontal and cingulate areas have been found to be down-regulated during the anticipation of a learned and predictable pain stimulus, possibly to distract sensory processing from the pain source (Hsieh *et al.*, 1999). Finally, it should be noted that EEG techniques are mostly sensitive to the activity of dorsolateral rather than deep areas of the cerebral cortex. Therefore, we could not disentangle in space local fine responses of cingulate areas preceding a repetitive and 'highly predictable' painful phasic stimulation. The present results need to be confirmed by neurophysiological techniques having a higher spatial resolution such as functional magnetic resonance imaging or positron emission tomography.

The negligible effect of pain expectancy on anticipatory negative ERPs (SPN) and HRD may be due to the repetitive/predictable features of the painful stimuli and to their poor information content, i.e. the stimuli conveyed neither feedback nor instructions. Furthermore, they did not determine an emotional/alertness 'breakdown' in our subjects as revealed by HRD. This explanation is consistent with the same lack of difference of low-band alpha EEG oscillations (6–10 Hz) over the cingulate cortex, which are sensitive to changes in alertness (Klimesch *et al.*, 1996; Klimesch, 1996, 1997, 1999). The basis of this explanation also relies on the bulk of previous evidence showing that anticipatory negative ERPs mainly reflect the emotional–motivational colouring of the upcoming stimulus (Böcker & van Boxtel, 1997; Böcker *et al.* 2001; Kotani *et al.* 2001). These potentials have negligible amplitude if the upcoming stimulus provides no feedback or instructions (Chwilla & Brunia, 1991) and does not trigger a motor reaction (van Boxtel & Brunia, 1994; Brunia & van Boxtel 2001). Further support for such an explanation comes from a parallel EEG study using a variant of the present experimental design (unpublished data). In that study, the galvanic stimulation was immediately followed by a visual stimulus triggering a Go/No go task. The results showed anticipatory negative ERPs, thus confirming that these potentials are mainly modulated by stimuli important for the regulation of action (Filipovic *et al.* 2001; Mnatsakanian & Tarkka, 2002).

Conclusions

In the present high-resolution EEG study, anticipatory cortical responses were modelled during the expectancy of predictable painful stimuli by means of the alpha ERD and the anticipatory negative ERPs (SPN). Compared with the control condition (non-painful stimulation), a progressive reduction of the alpha power was recognized over primary somatosensory cortex from 2 s before the painful stimulation. In contrast, the anticipatory ERPs were negligible during the expectancy period. The results on the alpha power suggest that the expectancy of the painful stimulation specifically facilitated the somatosensory thalamocortical channel. As expected with predictable and repetitive stimuli, the associative frontal-parietal areas were not involved as revealed by a rough measurement of anticipatory cortical rhythmicity by EEG techniques. The present results also suggest that negative ERPs are modest during the expectancy of warned stimuli (even if painful) with a simple information content.

Further investigations should evaluate whether the anticipation of pain is diversely represented when the painful stimuli are delivered at the left or right hand and whether the anticipatory cortical mechanisms are abnormal in chronic pain patients (i.e. maladaptive plasticity).

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Abbreviations

EEG, electroencephalography; ERD, event-related desynchronization; ERP, event-related potential; ERS, event-related synchronization; HRD, heart rate deceleration; IAF, individual alpha frequency; PSD, power spectral density; SPN, stimulus-preceding negativity.

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