

Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects

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Abstract

The dynamics of cortex driven by painful median nerve stimulation were investigated in event-related oscillation (ERO). We applied a wavelet time-frequency analysis to differentiate the brain dynamics between painful and non-painful somatosensory stimulation. The observed pattern to pain-induced effects exhibited a stepwise decrease of frequencies over time, starting around 26 ms over somatosensory cortex at 80 Hz, intermediate oscillations at 40 and 20 Hz around 40 ms, and reaching down to 10 Hz after 160 ms. This step-wise frequency decrease of ERO, coincident with spatial shift from the contralateral somatosensory area at 80 Hz to the centro-frontal brain at 40/20 Hz and final spatial expansion to the large region of centro-parietal areas at 10 Hz, may represent the cortical processes necessary to transfer sensory information from perceptual stages to subsequent cognitive stages in consciousness. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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Thalamocortical neurones are capable to produce spontaneously occurring fast oscillations, which closely resemble the induced gamma responses by external stimuli [19]. Further, both the spontaneous and induced fast polarization in the thalamic relay neurones are highly coherent with fast rhythms in cortical areas. These responses in the gamma frequency range (30–100 Hz) are considered a hallmark of brain activation pattern [19]. Induced gamma responses are part of event-related oscillations resonating between activity of single neurones and whole assemblies of neurones in a network of neocortex. Recently, it has been proposed [3] that selectively distributed electroencephalogram (EEG) oscillations in the delta, theta, alpha, beta, and gamma frequency range represent the activity of certain neural assemblies in a large web of neural networks. For example, the theta and gamma rhythms have been demonstrated to act as an integrated function in attention [14,17], short-term memory [18], perception [8,13], visual imagery [9,11], learning [10,15], and even pathological hallucination in schizophrenia [1]. Thus, event-related oscillation (ERO) in

the brain and its scalp EEG dynamics can be considered as probable correlates of sensory and cognitive functions [3,4,16].

The hypothesis of gamma rhythm and ERO in the brain for feature extraction and binding common features of an object from both local and widely distributed neural systems to generate one integrated percept demands a cohesive process of spatio-temporal dynamics of EEG resonance [3]. Although significant works on gamma-binding have been rapidly accumulated in the recent years [2], the cardinal feature of the binding hypothesis which states that ‘spatio-temporal dynamics of EEG rhythm at specific bandwidth acts as distributed information processing’ has rarely been demonstrated or unequivocally proven. Here, we report the characteristics of the spatio-temporal dynamics of event-related oscillation upon median nerve stimulation in human pain revealing such phenomena. Our analysis of the ERO in the well-controlled experimental noxious stimulation of the median nerve adds to the understanding of cortical processing of pain, and perhaps the conscious mechanisms, in man.

Informed written consent was obtained from each subject in accordance with the Helsinki Declaration. Somatosensory evoked potentials (SEPs) were recorded from 12

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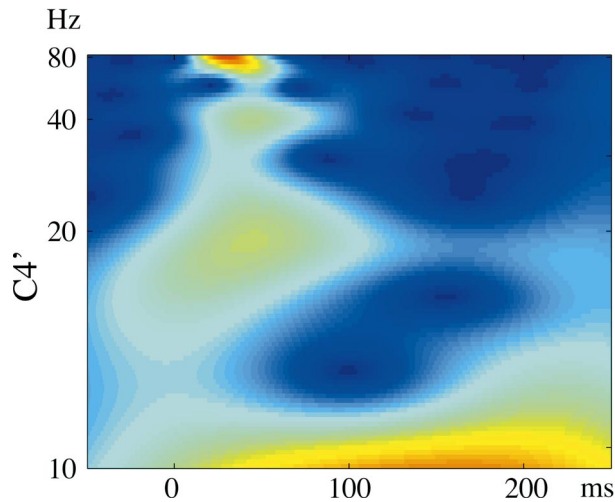


Fig. 1. Time-frequency plane of electrode $C4'$ (grand average across all subjects). Four individual frequency responses are evoked after stimulation: three early frequency components are at 80, 40 and 20 Hz and a late component at 10 Hz.

healthy, right-handed males (age: 26.8 ± 5.2) with 31 EEG and one electrooculogram electrodes (bandwidth 0.05–500 Hz, 2 kHz sampling, referenced to bilateral earlobes, impedance at $<5 \text{ k}\Omega$) in response to median nerve stimulation at the wrist of the left hand. Electrodes montage (cf. Fig. 2, upper left panel) followed the international 10–10 system and two extra electrodes ($C3'$ and $C4'$) were placed 2 cm posterior to $C3$ and $C4$, respectively. Baselines were computed (50 ms prior to stimulation) and subtracted before averaging. Epochs were scrutinized to be free from eye-movement and blink artefacts. Subjects were stimulated (600 trials, stimulation rate: 3 Hz) at two stimulation intensities (non-pain at $7.9 \pm 3.6 \text{ mA}$ and pain at $25.8 \pm 7.6 \text{ mA}$) tailored individually with an average of five trials by method ascending limit. The averaged SEPs (artefact-rejected, baseline-corrected, linear detrended) of each individual subject were then subjected to a wavelet analysis in order to investigate oscillatory activity. After wavelet transformation, averages were computed across subjects, as described recently [8]. It has been shown that the perception of sensory events is accompanied by the occurrence of responses in the alpha and beta range [5]. But, in addition, gamma-band activity also has been reported during the perception of sensory perception [6]. This led us to investigate individual frequency bands of our EEG data. In a first step we computed the time-frequency representation of electrode $C4'$ for frequencies in the range from 10 to 80 Hz. This was conducted by calculating the convolution of the SEP signal and a wavelet of a specific frequency. The amplitudes of the convoluted signals are colour-coded and integrated into the time-frequency plane (cf. Fig. 1). The SEP was convoluted with Morlet wavelets. In order to generate topographical maps of oscillatory activity, we extracted frequency lines from the time-frequency planes that represent the absolute amount of oscillations for all

electrodes in a certain period of time. We extracted only those frequencies at which activity actually occurred (80, 40, 20 and 10 Hz) that are shown in Fig. 2.

Selected electrode sites were pooled [12] to six topographical regions of interest (ROIs) in both hemispheres. The regions included the following electrodes, (e.g. ipsilateral left hemisphere): anterior region FP1, F7, F3, FC5; central region: $C3$, $C3'$, T3, PC5; posterior region: P3, T5, O1, PC1. Regions over the contralateral right hemisphere included the homologous electrodes. For statistical analyses amplitudes of oscillatory activity were pooled across the electrodes in each of the ROIs for each of the time intervals. Analysis of variances (ANOVAs) were computed for the following time intervals: 20–50 ms (early), 50–100 ms (middle) and 100–

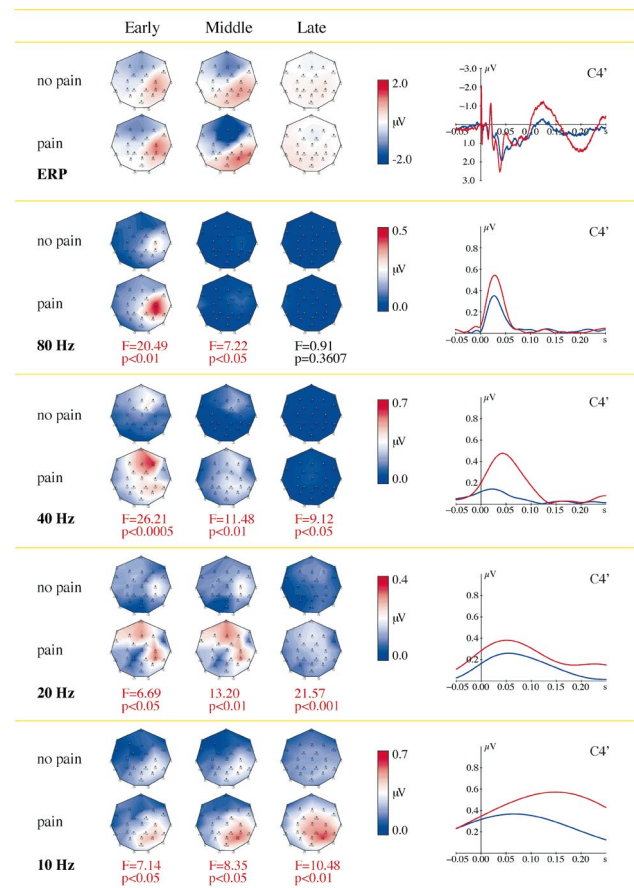


Fig. 2. Topographical distribution and time courses in response to painful and non-painful stimulation for the wide-band SEP response and the individual frequency bands. Maps are shown for the two conditions painful (lower row) and non-painful (upper row) stimulation. Each row of maps is split up into the three time intervals early (20–50 ms), middle (50–100 ms) and late (100–250 ms). Significant differences between conditions pain and no pain ($P < 0.05$) are indicated by red text. Time courses are also shown for painful (red) and non-painful (blue) stimulation. Top panel (SEPs): The maps for the wide-band (0.1–100 Hz) SEP response do not show clear differences between stimulation conditions while the time courses reveal especially a late differentiation. Oscillatory activity (lower panels) differentiate well between the two stimulation conditions.

250 ms (late). Repeated-measures ANOVAs with factors topography (anterior, central, posterior), hemisphere (left, right), frequency (80, 40, 20 and 10 Hz) and condition (pain, no-pain) were conducted to assess the effects of the experimental variables on a variety of dependent variables. All effects with more than two degrees of freedom in the numerator were adjusted for violations of sphericity which are inherent in repeated-measures analyses according to the formula of Geisser, and Greenhouse–Geisser epsilons were used to compute the *P*-values. Differences for the factor condition are shown in Fig. 2, while all other differences are reported in the text.

The time-frequency representation of the SEPs for electrode C4' revealed four individual activities at different frequencies, i.e. at 80, 40, 20 and 10 Hz (cf. red and yellow activity in Fig. 1). Maps were calculated for each of these frequencies to determine the individual topographic distributions of each frequency and time interval. Fig. 2 shows the topographic maps for all frequencies and for the unfiltered event-related potential (SEPs, top-right panel) for the time intervals early (20–50 ms), middle (50–100 ms) and late (100–250 ms). An ANOVA resulted in significant main effects of factors hemisphere (early: $F_{1,11} = 97.44$; $P < 0.0001$; middle: $F_{1,11} = 101.19$; $P < 0.0001$; late: $F_{1,11} = 16.03$; $P < 0.005$; always the contralateral right > the ipsilateral left), frequency (early: $F_{1,11} = 3.07$; $P < 0.05$; $10 > 40 > 20 > 80$ Hz; middle: $F_{1,11} = 19.43$; $P < 0.0001$; $10 > 20 > 40 > 80$ Hz; late: $F_{1,11} = 44.41$; $P < 0.0001$; $10 > 20 > 40 > 80$ Hz) and condition (early: $F_{1,11} = 21.24$; $P < 0.001$; middle: $F_{1,11} = 24.35$; $P < 0.0005$; late: $F_{1,11} = 14.23$; $P < 0.005$; always pain > no pain) for all time windows. In addition, significant interactions were found for topography*hemisphere (early: $F_{2,22} = 19.31$; $P < 0.0001$; middle: $F_{2,22} = 10.30$; $P < 0.001$), topography*frequency (early: $F_{6,66} = 4.48$; $P < 0.001$; middle: $F_{6,66} = 5.42$; $P < 0.001$; late: $F_{6,66} = 4.18$; $P < 0.05$), hemisphere*frequency (middle: $F_{3,33} = 10.34$; $P < 0.0001$; late: $F_{3,33} = 9.98$; $P < 0.0001$), topography*condition (middle: $F_{2,22} = 5.59$; $P < 0.05$; late: $F_{2,22} = 5.13$; $P < 0.05$), and frequency*condition (late: $F_{3,33} = 8.40$; $P < 0.05$). Post-hoc analyses for individual frequencies revealed significant main effects of hemisphere (contralateral > ipsilateral) for all frequencies and time intervals except the late 40 Hz and the middle and late 80 Hz where virtually no activity was present. Main effects for topography were only found significant in the middle time interval for 10 and 20 Hz. Main effects of condition are printed below the maps in Fig. 2. Significant interactions of topography*hemisphere were found for 10, 20 and 80 Hz in the early and for 10 Hz in the middle time interval. An interaction of hemisphere*condition was found to be significant only for the early time interval of the 80 Hz response. The latency of the amplitude maxima of all frequency components were located and summarized in a Fig. 3.

As early as 26 ms after stimulation, the difference

	F4	C4	P4	O2
10 Hz	237	160	141	112
20 Hz	74	46	54	76
40 Hz	38	44	43	44
80 Hz	38	30	26	37

Fig. 3. Latency of maxima in four electrodes over the right hemisphere for all investigated frequency bands. Solid arrows indicate a possible path of propagation of brain electrical activity through space and frequency. Electrodes, which are activated almost simultaneously, are shaded grey. The electric response of the brain to somatosensory stimulation is first recorded under electrodes C4'/P4 at 26/30 ms in the 80 Hz frequency range and then spreads from there to more frontal and more posterior regions. The earliest maximum of the 40 Hz activity is at the same electrode as the latest maximum of the 80 Hz activity (F4), indicating a down-modulation of the frequency. The latest maximum of this 40 Hz activity at 44 ms is again the earliest maximum of the 20 Hz activity in the same electrode (C4'). When the 40 Hz activity reaches O2 it is finally down-modulated to 10 Hz activity. Propagation through the brain is indicated by horizontal arrows, and down-modulation of the frequency by vertical arrows. The temporal propagation clearly involves the step-wise transitions from 80 to 40 to 20 to 10 Hz.

between pain and non-pain was most pronounced in the 80 Hz activity in the hand area over C4' contralateral to the stimulated hand with a very focal central-parietal topography. Following this early activation, a 40 Hz activity peaked at 44 ms and was significantly higher for the pain condition at the same site in C4'. This activity had two foci in frontal and central regions. Immediately after that, an ensuing 20 Hz activity peaked at 46 ms which was again higher for the pain condition than the no-pain condition, with a fronto-central topography around C4'. While the frontal activity was bilateral, the central activity was only present over the stimulated sensory area. Finally, the 10 Hz activity had its maximum in the late time window at 160 ms (C4'). The 10 Hz topography was centro-parietal, had its maximum over the contralateral right hemisphere and covered the largest region over the scalp.

The results of the peaks of the individual frequency components showed a clear increase in latency while the frequency decreased (cf. right column of Fig. 2). The 80 Hz activity peaks 26 ms after stimulation, 40 Hz after 43 ms, 20 Hz after 46 ms and 10 Hz after 112 ms. We summarized this stepwise decrease of frequency over time and topography in Fig. 3. Black arrows indicate a possible path through frequencies and brain. The activity starts over somatosensory brain early after stimulation and covers

only this primary somatosensory brain. Then the activity is propagated to frontal brain. There it was down-modulated to 40 Hz and spread towards more posterior regions again. When the 40 Hz activity reached somatosensory cortex, it was being down-modulated to 20 Hz and spread to more posterior regions. There it was down-modulated to 10 Hz, remaining in posterior regions.

Our findings showed shifts in frequencies in the electric activity of neural ensembles. It has been shown how initial gamma oscillations are being down-modulated to beta oscillations in in-vitro studies [20]. These findings indicate that during the time course of perception there is a spreading of electrical activity starting at higher frequencies and being down-modulated to sub-harmonic frequencies. Our results show that this is even true for a much broader range of frequencies, starting very locally at 80 Hz and ending rather wide-spread at 10 Hz. In addition, we also found a frontal/parietal 40 Hz response that has been hypothesized as conscious somatic perception [7]. After 26 ms, only somatosensory cortex contralateral to the stimulated hand (hemisphere*condition interaction) is activated at 80 Hz. Then the activity is down-modulated in frequency and spreads over brain. It is possible that the frequency of the EEG activity needs to be down-modulated to lower frequencies in order to activate large parts of the brain. Initial high frequencies may be capable of binding across small areas only, while lower frequencies can evoke synchronous activity in larger areas.

Time-frequency analysis of EEG proves to be highly sensitive in differentiating painful from non-painful somatosensory stimulation. This study established a spatio-temporal EEG frequency resonance model in sensory processing. Early processes are fast and focal while later processes spread out spatially and temporally. This could be due to different neural oscillators, which trigger each other and propagate their activity over the brain.

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