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Involuntary orientation of attention to unattended deviant nociceptive stimuli is modulated by concomitant visual task difficulty. Evidence from laser evoked potentials

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Abstract

Objective: Recent laser evoked potential (LEP) studies showed that unattended rare intensity-deviant nociceptive stimuli enhance the LEP vertex positivity P2 ('P400 effect'). It was hypothesized to reflect an involuntary switch of attention to nociceptive events. If true the P400 effect (1) should be produced when attention is focused on a task in another sensory modality (primary task), and (2) should be modulated by the primary task difficulty.

Methods: Subjects had to count the number of visual symbols presented on a screen. In a difficult condition, symbols were digits 1–4 (interference between amount and meaning). In an easy condition, symbols were letters X (no interference). Nociceptive CO_2 laser stimuli were simultaneously delivered on the left hand. Occasional stronger deviant stimuli (16%) were presented at random. In additional sessions, the strong stimuli were presented alone in homogenous series (100%).

Results: LEP amplitude at about 400 ms was larger for rare deviant than for homogenous stimuli. Visual task difficulty decreased LEP amplitude at this latency. Deviant stimuli seemed also to interfere with performance in the visual task.

Conclusions: The results give evidence for considering the P400 effect as reflecting an involuntary attentional shift to nociceptive events.

Significance: The study provides electrophysiological evidences for an intrusive capacity of pain to attract attention and to decrease behavioural performance in concurrent processes. In turn, such an attentional shift is tampered if attention is very engaged in a concomitant task.

Keywords: Pain; Laser evoked potentials; P400 effect; P3a; Attention; Distraction

1. Introduction

Pain is a complex subjective experience emerging from the processing of a large-scale network in the central nervous system. The modulation of this nociceptive system by high-order cognitive factors, such as attention, has been investigated in numerous experimental studies (see Eccleston and Crombez, 1999; Rainville, 2002). Directing attention to non-nociceptive stimuli or to another body area decreases detection performance of nociceptive stimuli

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; BA, Brodmann area; EEG, electroencephalogram; EOG, electro-oculogram; fMRI, functional magnetic resonance imaging; ISI, inter-stimulus time interval; LEF, laser-evoked magnetic field; LEP, laser-evoked potential; PET, positron emission tomography; SI, primary somatosensory cortex; SII, secondary somatosensory cortex.

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and pain reports (Bushnell et al., 1985; García-Larrea et al., 1997; Honoré et al., 1995; Miron et al., 1989; Peyron et al., 1999; Spence et al., 2002). Neuroimaging metabolic studies have reported that attentional modulation of nociception is accompanied by brain metabolic modification in various areas (Bantick et al., 2002; Brooks et al., 2002; Bushnell et al., 1999; Frankenstein et al., 2001; Longe et al., 2001; Petrovic et al., 2000; Peyron et al., 1999; Tracey et al., 2002; Valet et al., 2004). However, these studies were unable to relate each brain metabolic modification to specific attentional factors.

Because of their higher time resolution, electrophysiological experiments better succeeded at dissociating different sources of attentional modulation (see Lorenz and García-Larrea, 2003). Most of these studies used the laser evoked electrical potentials (LEPs) and magnetic fields (LEFs) (see Chen et al., 1998; Kakigi et al., 2000) to record responses of primary (SI) and secondary (SII) somatosensory, insular, anterior cingulate (ACC) areas (see García--Larrea et al., 2003) to selective activation of nociceptors (Bromm and Treede, 1984). For instance, modulation of nociceptive processing was observed as early as during N1, the first LEP component evoked by the Aδ-nociceptor activations—probably generated in SII (Frot and Mauguière, 2003; Vogel et al., 2003) and possibly also SI (Kanda et al., 2000; Schlereth et al., 2003; Tarkka and Treede, 1993)—when attention is spatially oriented or discarded (intramodal selective attention) from the stimulated body area (Legrain et al., 2002). Directing attention to non-nociceptive stimuli (intermodal selective attention) affected components of longer latency (García-Larrea et al., 1997; Yamasaki et al., 1999). Additionally to those top-down effects, it was also shown that, relative to frequently presented nociceptive stimuli, rare intensity-deviant stimuli increased amplitude of P2, a late vertex positivity supposed to reflect ACC activity (see García-Larrea et al., 2003), even when attention was directed away from the nociceptive stimuli (Legrain et al., 2002, 2003b). This difference between deviant and frequent stimuli, called the P400 effect, was hypothesized to be due to a P3a elicitation, an electrophysiological correlate of involuntary orientation of attention (Escera et al., 2000). This bottom-up effect allows the capture of attention, independently of voluntary control, by unexpected new potentially relevant events (Corbetta and Shulman, 2002; Näätänen, 1992). If true, the study of such LEP activities may allow to better understand how nociceptive inputs catch attention and enter into consciousness as pain perception.

Previous studies dissociated involuntary orientation of attention effect from selective attention effect on nociception. The aim of the present study was to give evidence for close interaction between top-down and bottom-up factors for orienting attention toward or away from nociceptive events. Although P3a is elicited by novel/deviant stimuli even when attention is withdrawn and focused on another task (the primary task), it is dependent on top-down factors: its amplitude decreases when the primary task is more difficult to perform (Berti and Schröger, 2003; Harmony et al., 2000), indicating that the more the primary task demands are important (in terms of attentional resources), the less resources are available for orienting attention to unexpected new/deviant events (Siddle, 1991). If the nociceptive P400 effect results from a P3a-like process, this effect (1) should be observed when subject's attention is directed toward a pain-unrelated task and (2) should be modulated by the difficulty of that task. In other words, amplitude increase at P2 latency should be observed for rare unattended deviant laser stimuli, and such an increase should be modulated by task difficulty. These hypotheses were tested with nociceptive laser stimuli in an 'ignore' oddball situation (Squires et al., 1975) while subject's attention was focused on a visual task. The visual task was made of two conditions: a difficult condition with cognitive interference and a less demanding easy condition (Bush et al., 1998).

2. Materials and methods

2.1. Subjects

Ten paid right-handed subjects (five men, five women, 25 ± 2 years of age) participated to the study with given informed consent. They had no prior history of neurological, psychiatric or chronic pain disorder, and did not take psychotropic medication.

2.2. Stimuli

Subjects received sixteen blocks of 60 visual and 50 nociceptive stimuli each, during two sessions (with half of the blocks each) separated by at least one day. Visual stimuli were centrally presented on a 17 inches monitor at a distance of $\sim$107 cm in front of the subjects. Each stimulus consisted of one, two, three or four symbols displayed horizontally. Symbol size on the screen was 30 mm high and 20 mm wide, and distance between symbols was 18 mm. Stimulus duration was 1470 ms, inter-stimulus time interval (ISI) was 1100 ms (offset to onset). In eight blocks (easy condition), symbols were X letters. In the eight remaining blocks (difficult condition), symbols were the digits 1, 2, 3 or 4. Stimulus contained only one digit type, and the number of digits was never congruent with digit meaning (e.g. 4 was presented one, two or three times, but never four times).

Nociceptive stimuli were delivered on the dorsum of the left hand by a CO_2 laser (Department of Physics, Université catholique de Louvain, Belgium) with 10.6 μm wavelength and 25 W maximum output power. Stimulus impact was visualized by means of a coaxial He–Ne laser beam. Stimulus duration was 50 ms, and stimulus surface area was 80 mm^2. The laser beam was slightly moved between each

stimulus in order to minimize habituation or nociceptor sensitisation. Fourteen from the sixteen blocks (oddball series) contained 42 weak intensity (~500 mJ) and eight strong intensity (~750 mJ) deviant stimuli. Intensities were settled above Aδ-fiber activation threshold in order to obtain bearable pinprick sensations and a late LEP complex. Stimuli were randomly delivered with the restriction that a strong deviant stimulus followed at least two weak stimuli. The two remaining blocks (homogenous series) contained 50 stimuli of strong intensity (~750 mJ). As stimulus intensity strongly affects LEP amplitudes and latencies (e.g. Bjerring and Arendt-Nielsen, 1988; Carmon et al., 1976; Iannetti et al., 2005; Kakigi et al., 1989; Plaghki et al., 1994), homogenous series were introduced in order to match stimulus intensity for comparison of probability effects (deviant vs. standard). The thermal drift of the laser equipment increased stimulus intensity by less than 5%. ISI was 3 s, so laser stimuli were not time-locked to the visual stimuli. This was done in order to avoid contamination of LEPs by visual brain activity.

2.3. Procedure

Subjects were seated on a chair in an air-conditioned room (22–24 °C). To avoid any environmental clue, the instruments and the left hand were hidden from subject's view by a shield, and background noise was diffused through earphones. Seven oddball series and one homogenous series were presented during each of the two (easy and difficult) visual conditions. Only two homogenous series were used in order to obtain an equivalent amount of EEG epochs for averaging per condition. Each block lasted 2 min 40 s and blocks were separated by ~3 min break (10 min between fourth and fifth blocks). During the first session, experimental blocks were preceded by one block with 5–10 stimuli of increasing intensity in order to familiarize the subjects with laser stimuli, and one trial block with 10 weak laser stimuli and 12 visual stimuli of the easy condition. Experimental blocks were randomly assigned. Subjects were asked to pay attention to the visual stimuli and to count the number of symbols displayed on the screen regardless of their meaning. They responded with their right hand by means of a four-keys pad. They were instructed to respond as accurately and as fast as possible. Subjects were informed that laser stimuli were delivered as distractors in order to increase task difficulty, and were encouraged to disregard laser stimuli and to focus on the visual task. They were not informed about deviant laser stimuli.

2.4. Recording

Performance in the visual task was measured by reaction times and error percentages. Electroencephalogram (EEG) (PL-EEG, Walter Graphtek, Germany) was recorded by 19 Ag–AgCl electrodes placed according to the 10–20 International System and referenced to linked earlobes (ground at the right wrist, electrode impedance below 5 kΩ, sample rate 167 cps, 3 s time constant, gain of 1000, 0.06–75 Hz band filters, 50 Hz notch filter). Vertical and horizontal electro-oculogram (EOG) was recorded from two Ag–AgCl electrodes placed diagonally up and down the right eye. EEG epoch time window lasted from −500 ms to 2566 ms. Epochs were off-line filtered with a 0.1–20 Hz bandpass (24 dB/octave), corrected for DC shift, EOG artefacts, and baseline (−500 to 0 ms) (Scan 3.0, Neuroscan, USA). After artefact rejection, epochs recorded in response to strong intensity stimuli were averaged according to experimental conditions. As LEP amplitudes and latencies are affected by stimulus intensity, EEG responses to weaker stimuli were not taken into account for analysis. Electrodes F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4 and T6 were used for analysis.

2.5. Data analysis

Reaction times and error rates were submitted to a two-factors ANOVA for repeated measures with laser stimuli series (oddball vs. homogenous) and visual task difficulty (easy vs. difficult) as factors. Amplitude and latency of LEPs to strong laser stimuli were submitted to a four-factors ANOVA with two additional factors for scalp topography analysis. These two factors represent electrode sites across the coronal (frontal, central, parietal) and the sagittal lines (left lateral, left medio-lateral, median, right medio-lateral, right lateral) (see bottom illustration on Fig. 5). Topographical differences between conditions were also assessed after amplitude normalization by the vector length method (McCarthy and Wood, 1985). When appropriate, Greenhouse–Geisser correction of degrees of freedom and contrast analyses of means were used. Significance level was set at $P<0.05$.

P2 was identified at Cz as a positive component between 300 and 450 ms. N2 was defined at Cz, and also at C4 and T4 (see Legrain et al., 2002), as the negative component preceding the positivity between 200 and 270 ms. N1 was defined at C4 and T4 as the negative component preceding N2 between 120 and 200 ms. Latencies were measured from stimulus onset to peak, and amplitudes from peak to the 500 ms pre-stimulus baseline.

3. Results

3.1. Behavioural data

Reaction times to visual stimuli (Fig. 1) were shorter during the easy condition than during the difficult condition ($F_{1,9}=149.44$, $P<0.001$). They were larger during presentation of the oddball laser series than during the homogenous series ($F_{1,9}=5.29$, $P=0.047$). Stimulus series did not affect error percentage ($F_{1,9}=0.35$, $P=0.571$) while

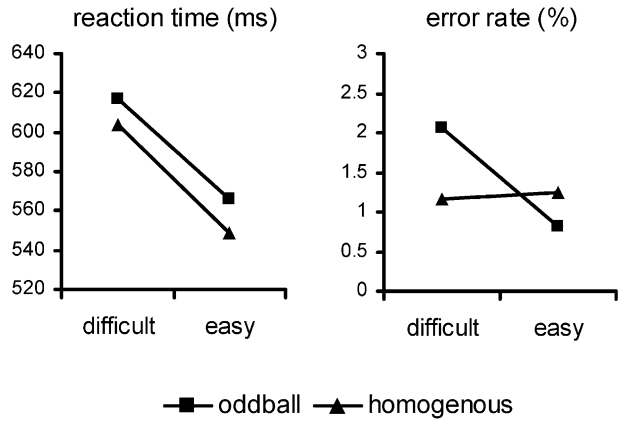

Fig. 1. Behavioural performances (reaction times and error rates) for the easy and difficult visual task conditions according to laser stimulus series.

the effects of task difficulty and the interaction approached the significance level ($F_{1,9}=4.76$, $P=0.057$ and $F_{1,9}=5.02$, $P=0.052$, respectively): in oddball laser series, subjects made slightly more errors during the difficult condition than during the easy condition ($F_{1,9}=9.66$, $P=0.012$), while there was no difference in homogenous laser series ($F_{1,9}=0.04$, $P=0.840$).

3.2. Electrophysiological data

LEPs in response to strong intensity nociceptive stimuli are shown on Fig. 2. P2 was identified at about 400 ms and labeled 'P400'. It displayed its maximal amplitude at the vertex (Fig. 3). It was not followed by any identifiable positive component. P400 was preceded by a negativity at about 250 ms ('N250') in nine of the ten subjects. No contralateral negativity (N1) could consistently be identified, even with frontal reference (see Kunde and Treede, 1993).

P400 amplitude was significantly larger for oddball deviant than for homogenous series ($F_{1,9}=23.23$, $P=0.001$), and larger during the easy condition than during the difficult visual condition ($F_{1,9}=24.44$, $P=0.001$) (Fig. 4). The interaction between both factors was significant ($F_{1,9}=5.74$, $P=0.040$): amplitude difference between deviant and homogenous stimuli was larger during the easy ($F_{1,9}=75.84$, $P<0.001$) than the difficult task ($F_{1,9}=28.31$, $P<0.001$). P400 to deviant stimuli was larger during the easy task than during the difficult task ($F_{1,9}=28.25$, $P<0.001$), while this difference was not significant for homogenous stimuli ($F_{1,9}=3.72$, $P=0.086$). Nevertheless, the task effect for homogenous laser stimuli was significant at median ($F_{1,9}=5.34$, $P=0.042$) and medio-lateral ($F_{1,9}=3.95$, $P=0.050$) and not at lateral lines ($F_{1,9}=2.88$, $P=0.111$). There were significant main effects of the topographical factors (coronal: $F_{2,15}=21.69$, $P<0.001$; sagittal: $F_{4,36}=132.86$, $P<0.001$; interaction: $F_{8,72}=6.14$, $P<0.001$). This was confirmed with normalized data (coronal: $F_{2,14}=20.54$, $P<0.001$; sagittal: $F_{4,36}=139.89$, $P<0.001$; interaction:

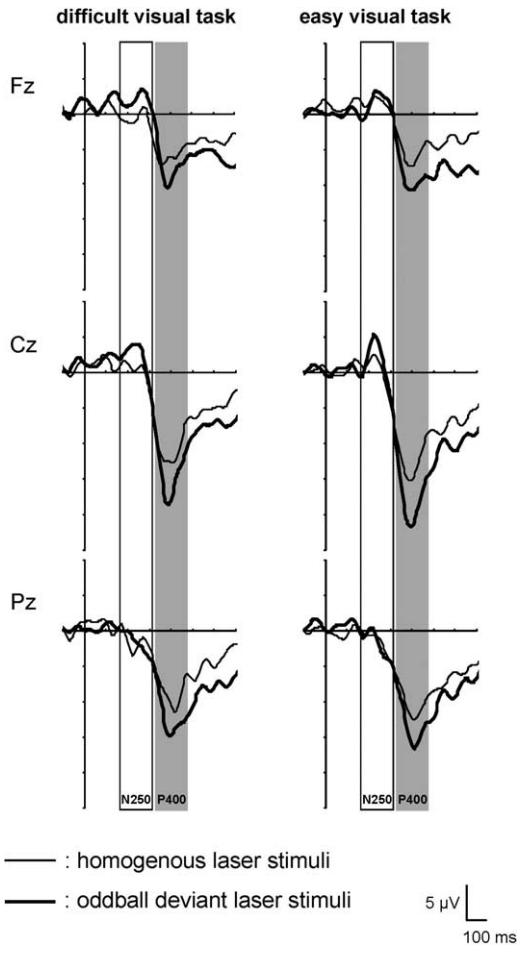

Fig. 2. Grand-average LEPs following strong intensity oddball deviant (thick traces) and homogenous stimuli (thin traces), during the difficult (left) and the easy (right) task conditions. White and grey boxes show the time-window of N250 and P400 components, respectively.

$F_{8,72}=6.39$, $P<0.001$) (Fig. 5). In summary, these effects revealed that P400 amplitude was greatest at the vertex: it was larger on central than on parietal electrodes (only on median electrodes [Cz–Pz]: $F_{1,9}=14.45$, $P=0.003$), and

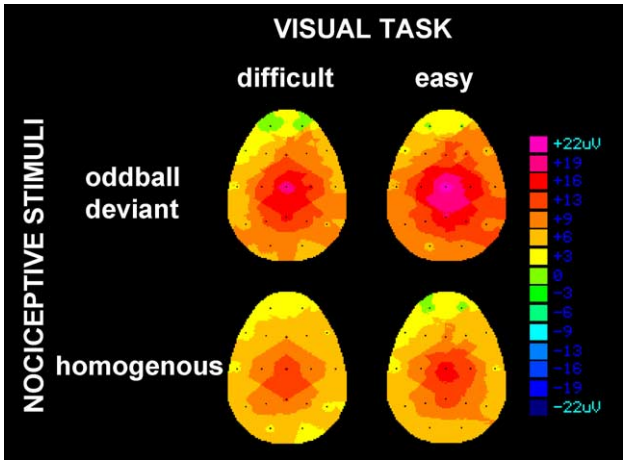

Fig. 3. Grand-average scalp topographical maps at P400 peak amplitude.

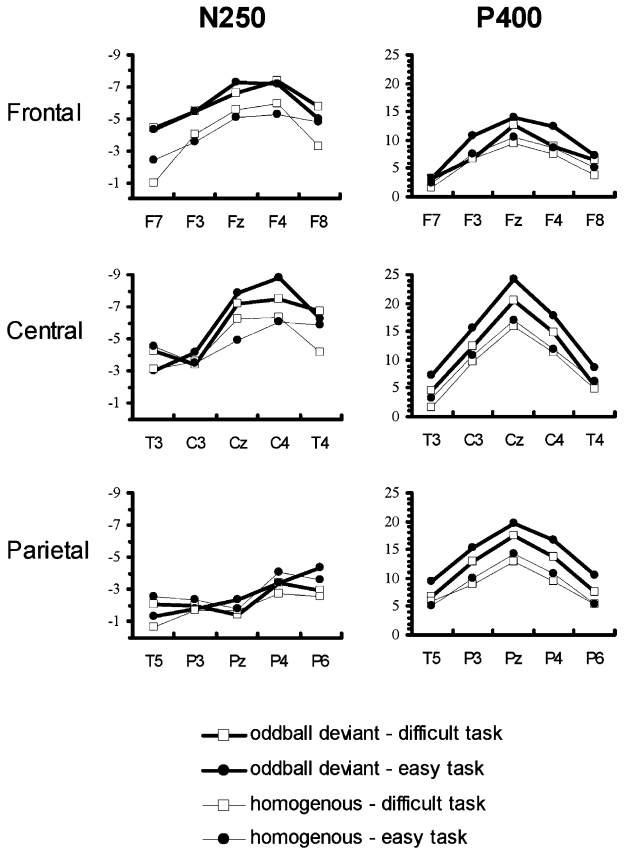

Fig. 4. Mean amplitudes (μV) for N250 and P400 for the four experimental conditions.

larger on parietal than on frontal electrodes (with some exceptions for lateral electrodes), and decreased from median to lateral electrodes (all contrasts, $P \leq 0.045$). Finally, amplitudes were significantly larger on right than on left hemisphere ($F_{1,9} = 17.27$, $P = 0.005$), excepted at parietal electrodes ($F_{1,9} = 0.93$, $P = 0.207$).

With significant main effects of the coronal ($F_{2,14} = 5.99$, $P = 0.019$) and the sagittal ($F_{4,36} = 15.55$, $P < 0.001$) topographical factors, P400 latency was later at parietal than at frontal electrodes ($F_{1,9} = 11.77$, $P = 0.007$), and later at lateral than at all other electrodes (all contrasts, $P \leq 0.003$). The effects of the experimental factors were not significant (laser: $F_{1,9} = 0.38$, $P = 0.554$; task: $F_{1,9} = 0.89$, $P = 0.372$; interaction: $F_{1,9} = 1.05$, $P = 0.333$).

For N250 amplitudes, there was no significant effect for the experimental factors (laser series: $F_{1,8} = 1.68$, $P = 0.232$; visual task: $F_{1,8} = 0.40$, $P = 0.545$; interaction: $F_{1,8} = 0.05$, $P = 0.826$) (Fig. 4). But both factors interacted together with the sagittal factor at a nearly significant level ($F_{2,18} = 3.15$, $P = 0.064$). This interaction is illustrated on Fig. 6, and is due to some differences between experimental conditions at median and right sagittal lines. Topographical factor effects were significant with raw (coronal: $F_{2,14} = 11.89$, $P = 0.001$; sagittal: $F_{1,11} = 6.66$, $P = 0.021$; interaction: $F_{8,64} = 4.68$, $P < 0.001$) and normalized data (coronal: $F_{2,14} = 12.32$, $P = 0.001$; sagittal: $F_{1,11} = 6.73$, $P = 0.020$; interaction: $F_{8,64} = 4.52$, $P < 0.001$) (Fig. 5), suggesting larger amplitude on right than on left hemisphere ($F_{1,8} = 20.32$, $P = 0.006$) and

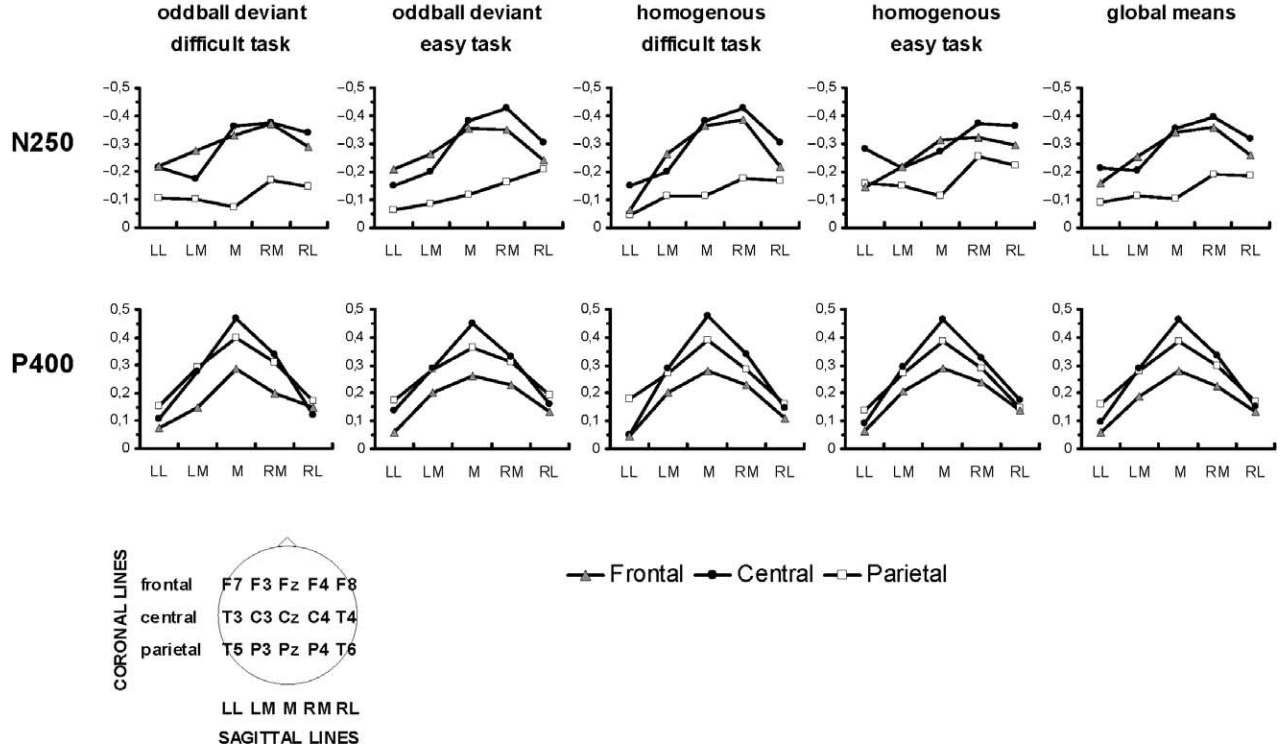

Fig. 5. LEP scalp topography from normalized amplitudes, for each experimental conditions and for global mean across conditions (right graphics). The bottom picture illustrates organization of electrode sites by the coronal and the sagittal factors. LL, left lateral; LM, left medio-lateral; M, median; RM, right medio-lateral; RL, right lateral.

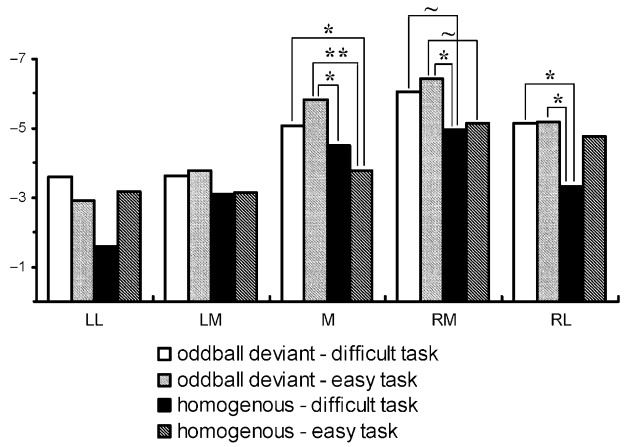

Fig. 6. Comparison of experimental condition effects on N250 amplitude (μV) for each sagittal lines (global mean across coronal lines). LL, left lateral; LM, left medio-lateral; M, median; RM, right medio-lateral; RL, right lateral. ∼, $P \leq 0.060$; *, $P \leq 0.050$; **, $P \leq 0.010$; ***, $P \leq 0.005$.

smaller amplitude on parietal than on frontal ($F_{1,8}=15.05$, $P=0.002$) and central sites ($F_{1,8}=19.84$, $P<0.001$).

N250 latency was ∼10 ms longer during the difficult than during the easy task conditions ($F_{1,8}=6.68$, $P=0.032$) at median and medio-lateral sites ($F_{3,24}=3.13$, $P=0.045$; all contrasts, $P \leq 0.003$). Significant main effects of the topographical factors (coronal: $F_{2,15}=4.33$, $P=0.034$; sagittal: $F_{4,32}=7.10$, $P<0.001$) revealed shorter N250 latencies at central than at parietal electrodes ($F_{1,8}=8.65$, $P=0.010$) and shorter latencies on the right than on the left hemisphere ($F_{1,8}=26.16$, $P=0.003$).

4. Discussion

In the present study, we hypothesized that rare deviant nociceptive stimuli would produce a P3a-like response during the P2 time-window. More precisely, it was predicted that such a response (1) should be observed when subject's attention is directed toward a pain-unrelated primary task and (2) should be modulated by the primary task difficulty. In that task, subjects counted the number of symbols on each visual display. In the difficult condition, symbol meaning interfered with symbol amount, while there was no interference in the easy condition. Reaction times were prolonged in the difficult condition as cognitive interference resolution engaged more attentional resources (see Bush et al., 1998).

4.1. The P400 effect reflects involuntary orientation of attention

While N250 (N2) was not significantly affected by experimental conditions (see also Kanda et al., 1996; Legrain et al., 2002, 2003a,b; Plaghki, 1997; Towell and Boyd, 1993), results show that strong intensity deviant nociceptive stimuli elicited P400 (P2) with larger amplitude as compared to nociceptive stimuli of the same intensity delivered in homogenous series, both in difficult and easy visual task conditions (bottom-up effect). These results confirm those observed in our previous studies (Legrain et al., 2002, 2003b) in which LEP amplitude increase was observed at the P2 latency for intensity-deviant stimuli, even when spatial attention was directed to the non-stimulated hand. Next, P400 (P2) amplitude was decreased when the difficulty of the visual task was increased. Furthermore, laser stimulus series and visual task conditions interacted together: amplitude difference between task conditions was weaker for homogenous than for deviant stimuli. It suggests that visual task conditions affected more LEP responses to deviant than to homogenous laser stimuli. As a consequence, the P400 effect—in other words P400 amplitude increase by deviant stimuli—was larger when visual task was more difficult (top-down modulation of the P400 effect). Finally, as in the previous studies, P400 (P2) amplitude was maximal at the vertex and decreased progressively on sagittal and coronal lines. The more striking point is that neither P400 (P2) scalp topography nor its latency were affected by experimental conditions.

LEP amplitude increase at the P2 latency was also observed for location-deviant laser stimuli during oddball paradigm when subjects were actively counting the frequent stimuli (Zaslansky et al., 1996), while counting deviant stimuli elicited a P3b-like parietal positivity indexing the closure of the processing of the task-relevant event (Kanda et al., 1996; Legrain et al., 2003a; Opsommer et al., 2003; Plaghki, 1997; Siedenberg and Treede, 1996; Towell and Boyd, 1993). As the laser-P3b has a longer latency (∼600 ms), and as it was observed neither in present study, nor in the previous studies for deviant stimuli presented outside the focus of spatial attention (Legrain et al., 2002, 2003b), the P400 effect was not due to a P3b-like response. So, the P400 effect seems well to correspond to the fronto-central P3a component indexing an involuntary shift of attention to new/deviant events (Escera et al., 2000). P3a is evoked by sudden unexpected rare novel or deviant (as compared to environmental background stimuli or ongoing cognitive activities) auditory, visual and somato-sensory stimuli (Alho et al., 1998; Bruyant et al., 1993; Daffner et al., 2000; Escera et al., 1998; Harmony et al., 2000; Katayama and Polich, 1998; Mecklinger et al., 1997; Schröger and Wolff, 1998; Squires et al., 1975; Woods, 1992; Yago et al., 2003). Unlike P3b, P3a is evoked even when the subjects do not pay attention to the stimulus series (Squires et al., 1975), but its amplitude is modulated by attention (Alho et al., 1998; Escera et al., 1998; Mecklinger et al., 1997). For example, Woods (1992) observed P3a in response to new and deviant auditory stimuli as well inside and outside the focus of spatial attention, with larger amplitude inside the focus of spatial attention. On the other hand, P3a amplitude is decreased by primary task complexity (Berti and Schröger, 2003; Harmony et al., 2000).

P3a amplitude is larger for particularly salient stimuli such as new, non-familiar stimuli or stimuli interfering with task-relevant stimuli (Daffner et al., 2000; Escera et al., 1998; Mecklinger et al., 1997; Schröger and Wolff, 1998). Most of these features were observed for the nociception-related P400 effect: this effect was observed (1) for rare deviant nociceptive stimuli, (2) especially when they are more salient such as stronger-intensity stimuli, (3) even when attention is withdrawn, or (4) when these stimuli are not relevant for current cognitive goals (Legrain et al., 2002, 2003a,b).

The present study adds new findings by showing that the P400 effect is modulated by the difficulty of the primary task. The P400 effect was observed at P2 latency where amplitude was enhanced by deviant stimuli as compared to homogenous stimuli when subject's attention was directed to visual stimuli, and this P400 effect was smaller during the difficult than during the easy visual task condition. This suggests that when subjects are distracted from painful stimuli, attention can be involuntarily re-oriented by sudden and unexpected nociceptive stimuli (bottom-up effect). However, as orienting is not purely reflexive but also contingent on voluntary control (Pashler et al., 2001), involuntary attentional orientation to nociceptive stimuli depends on the attentional workload of primary cognitive goals and amount of attentional resources available (top-down modulation of orienting response) (Escera et al., 2000; Schröger, 1997; Siddle, 1991), and is less important when subjects are engaged in a very demanding task such as dealing with cognitive interference.

4.2. The P400 effect does not reflect top-down modulation of sensory processing

In the present study, primary task difficulty also affected amplitude of the positivity evoked by homogenous stimuli, but to a lesser extent: amplitude difference was weaker and only significant at median and medio-lateral electrodes. The laser P2, recorded in non-oddball condition, was also modulated by attention when subjects operate selection between nociceptive stimuli and stimuli from another sensory modality (Beydoun et al., 1993; Friederich et al., 2001; García-Larrea et al., 1997; Yamasaki et al., 1999). So, it could be argued that task difficulty modulated sensory brain response to nociceptive inputs independently of orienting mechanisms. However, in the present study, stimulus type and task complexity interacted: visual task conditions affected more LEPs to deviant stimuli, as a larger amplitude difference between easy and difficult conditions was observed for the deviant stimuli than for the homogenous stimuli. As a consequence, the P400 effect was larger in the easy than in the difficult task conditions. So, such a difference was probably mainly produced by modulation of attentional orientation-related processes. The results suggest that task difficulty affected both nociceptive 'exogenous' and nociception-triggered attentional processes, with greater effect for attentional processes.

4.3. The P400 effect does not reflect habituation of sensory processing

Homogenous stimuli were presented in one trial block, separated by 3 s, and deviant stimuli were always preceded by at least two weaker stimuli, so that time interval between two deviant stimuli was much longer. Based on this, it can be argued that amplitude difference obtained at P2 latency between deviant and homogenous stimuli resulted from a difference in receptor fatigue and/or habituation. However, although habituation of laser P2 amplitude cannot be completely avoided, the following facts plead against this interpretation for the P400 effect. In the oddball series, deviant and frequent stimuli were presented on the same hand. The laser beam was moved between each stimulus. ISI was exactly the same for oddball and for homogenous series. There was no significant difference for N250 amplitude. Finally and most importantly, amplitude difference between difficult and easy task conditions was larger for deviant than for homogenous stimuli. If the P400 effect was only due to habituation, the primary task difficulty should have influenced LEP amplitudes to deviant and homogenous stimuli in the same way. So, it may be stated that amplitude difference obtained at P2 latency was primarily due to the deviancy and deviancy-triggered attentional orienting, and does not reflect faster P2 habituation for homogenous than for deviant stimuli.

4.4. Brain generators of the P400 effect?

In the present study and in previous ones (Legrain et al., 2002, 2003b), it was shown that the P400 waveform, latency and topography did not change across experimental conditions. This rises questions regarding the brain generators of the P400 effect. For instance, the P400 effect can reflect modulation of the laser P2 itself or that of a modality non-specific P3a component occurring at the same latency. The former hypothesis could imply that amplitude modulation of the laser vertex positivity itself, or at least some of its sub-components (Legrain et al., 2003a), reflects mainly attentional processes.

As a fact, numerous studies based on dipolar source modeling (Bentley et al., 2003; Bromm and Chen, 1995; Lenz et al., 1998; Schlereth et al., 2003; Tarkka and Treede, 1993; Valeriani et al., 2000) suggest an involvement of ACC—mainly the BA 24′ subsection (García-Larrea et al., 2003)—in the generation of the laser P2. On the other hand, it has been demonstrated in the visual and auditory modalities, that ACC is involved in the generation of the P3a component (Baudena et al., 1995; Ebmeier et al., 1995; Yago et al., 2003). ACC is assumed to play a role in novelty detection and orienting (Berns et al., 1997; Clark et al., 2000; Downar et al., 2000; Williams et al., 2000). Using nociceptive heat stimuli,

Peyron et al. (1999) showed haemodynamic increase in BA 24′ when attention was directed to auditory stimuli. The frontal-parietal network involved in involuntary attention (Corbetta and Shulman, 2002), including ACC (BA 24′), was also activated in response to sudden onset of painful thermal stimuli, but with prolonged activity as compared to non-painful stimuli (Downar et al., 2003). Finally, Bantick et al. (2002), using a task similar to the present one in a fMRI study, found a decreased response to nociceptive stimuli in BA 24′ when task demands increased. From this short review of recent literature, it may be suggested that the P400 effect reflects, at least in part, a modulation of ACC and represents possibly an electrophysiological correlate of orienting to nociceptive events.

4.5. Behavioural arguments for involuntary orientation of attention

Additionally to slower reaction times during the difficult than the easy task, laser deviant stimuli seem to produce distraction as reaction times were prolonged during presentation of the oddball laser series as compared to homogenous series. Deviant or novel auditory and visual stimuli, eliciting P3a, also produced distraction and decreased performance in the primary task (Berti and Schröger, 2003; Escera et al., 1998; Grillon et al., 1990; Schröger and Wolff, 1998). It is worth noting that intensities of deviant and homogenous laser stimuli were the same, and that homogenous series contained more strong intensity stimuli than oddball series. Then, it can be assumed that decreased performance in the visual task was due to actual orienting of attention to deviant nociceptive stimuli, with less influence of their intensity.

Increase of error rate seems to depend on the laser stimulus series. Indeed, subjects made more errors in the difficult condition during presentation of the oddball series, while there was no difference during homogenous series. Then, it is possible that nociceptive stimuli brought more distraction in the difficult condition when they were presented as deviant with weaker stimuli. However, if P400 effect reflects attentional re-orienting from visual to nociceptive stimuli, the more distracting effect of deviant laser stimuli during the difficult task condition is not consistent with electrophysiological data and with the hypothesis of a greater orienting response for deviant stimuli during the easy task condition. A way to conciliate this point is to suggest that the task condition without visual interference was easy enough to allow attentional orienting toward laser stimuli without affecting task performance (see Schröger, 1997). On the other hand, in the difficult task condition, the competition for attentional resources was much more important between nociceptive and visual stimuli, leading to performance decrease on visual stimuli even with less orienting toward laser stimuli.

Behavioural results were not clearly significant and need to be replicated with control over the number of experimental blocks and over the timing between task-relevant and deviant stimuli. Nevertheless, they offered some behavioural evidence, e.g. distraction, for the P400 effect as reflecting attentional orienting operations. Distraction in primary task produced by unexpected nociceptive events was already observed by other investigators (Arntz and Hopmans, 1998; Crombez et al., 1994; Lorenz and Bromm, 1997). The present study adds new findings by suggesting that distraction is probably due to involuntary attentional orientation. Several studies showed more distraction when it is produced by nociceptive stimuli and support the idea that attention is preferentially attracted by painful events when they interfere with the processing of other information (Crombez et al., 1996, 1997; Miron et al., 1989; Van Damme et al., 2002, 2004a,b; see Eccleston and Crombez, 1999). We hypothesize that the P400 effect, as probably reflecting involuntary attentional switching, mediated by ACC activity, may be the neurophysiological correlate of such an attentional priority for pain. As a basic function of pain is to alert of a potential source of danger, this P400 effect could reflect crucial brain processes disrupting current cognitive and behavioural activities, prompting selective processing of that source of danger, and allowing the preparation of better adapted behaviours such as limb withdrawal.

5. Conclusion

In addition to early attentional selective operations, the present LEP study revealed that attention can be involuntarily re-oriented toward nociceptive events at a later latency—as reflected by the P400 effect—even when attention was initially directed to visual stimuli. It was also shown that such an involuntary attentional switch is influenced by endogenous factors such as primary goal demands. This study provides first evidence for close interaction between bottom-up and top-down factors for orienting attention toward or away from nociceptive events.

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References

Alho K, Winkler I, Escera C, Huotilainen M, Virtanen J, Jääskeläinen IP, Pekkonen E, Ilmoniemi RJ. Processing of novel sounds and frequency changes in the human auditory cortex: magnetoencephalographic recordings. Psychophysiology 1998;35:211–24.

Arntz A, Hopmans M. Unpredicted pain disrupts more than correctly predicted pain, but does not hurt more. Behav Res Ther 1998;36: 1121–9.

Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310–9.

Baudena P, Halgren E, Heit G, Clarke JM. Intracerabral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 1995;94:251–64.

Bentley DE, Derbyshire SWG, Youell PD, Jones AKP. Caudal cingulate cortex involvement in pain processing: an inter-individual laser evoked potential source localisation study using head realistic models. Pain 2003;102:265–71.

Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science 1997;276:1272–5.

Berti S, Schröger E. Working memory controls involuntary attention switching: evidence from an auditory distraction paradigm. Eur J Neurosci 2003;17:1119–22.

Beydoun A, Morrow TJ, Shen JF, Casey KL. Variability of laser-evoked potentials: attention, arousal and lateralized differences. Electroencephalogr Clin Neurophysiol 1993;88:173–81.

Bjerring P, Arendt-Nielsen L. Argon laser induced single cortical responses: a new method to quantify pre-pain and pain perceptions. J Neurol Neurosurg Psychiatry 1988;51:43–9.

Bromm B, Chen ACN. Brain electrical source analysis of laser evoked potentials in response to painful trigeminal nerve stimulation. Electroencephalogr Clin Neurophysiol 1995;95:14–26.

Bromm B, Treede RD. Nerve fibre discharges, cerebral potentials and sensations induced by CO_2 laser stimulation. Hum Neurobiol 1984;3: 33–40.

Brooks JCW, Nurmikko TJ, Bimson WE, Singh KD, Roberts N. fMRI of thermal pain: effects of stimulus laterality and attention. NeuroImage 2002;15:293–301.

Bruyant P, García-Larrea L, Mauguière F. Target side and scalp topography of the somatosensory P300. Electroencephalogr Clin Neurophysiol 1993;88:468–77.

Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL. The counting Stroop: an interference task specialized for functional neuroimaging—validation study with functional MRI. Hum Brain Mapp 1998;6:270–82.

Bushnell MC, Duncan GH, Dubner R, Jones RL, Maixner W. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. J Neurosci 1985;5:1103–10.

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: is there a role for primary somatosensory cortex? Proc Natl Acad Sci USA 1999;96:7705–9.

Carmon A, Mor J, Goldberg J. Evoked cerebral responses to noxious thermal stimuli in humans. Exp Brain Res 1976;25:103–7.

Chen ACN, Arendt-Nielsen L, Plaghki L. Laser-evoked potentials in human pain. I. Use and possible misuse. Pain Forum 1998;7:174–84.

Clark VP, Fannon S, Lai S, Benson R, Bauer L. Responses to rare visual target and distractor stimuli using event-related fMRI. J Neurophysiol 2000;83:3133–9.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15.

Crombez G, Baeyens F, Eelen P. Sensory and temporal information about impending pain: the influence of predictability on pain. Behav Res Ther 1994;32:611–22.

Crombez G, Eccleston C, Baeyens F, Eelen P. The disruptive nature of pain: an experimental investigation. Behav Res Ther 1996;34:911–8.

Crombez G, Eccleston C, Baeyens F, Eelen P. Habituation and interference of pain with task performance. Pain 1997;70:149–54.

Daffner KR, Scinto LFM, Calvo V, Faust R, Mesulam MM, West WC, Holcomb PJ. The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. J Cogn Neurosci 2000;12: 393–406.

Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 2000;3:277–83.

Downar J, Mikulis DJ, Davis KD. Neural correlates of the prolonged salience of painful stimulation. NeuroImage 2003;20:1540–51.

Ebmeier KP, Steele JD, MacKenzie DM, O'Carroll RE, Kydd RR, Glabus MF, Blackwood DHR, Rugg MD, Goodwin GM. Cognitive brain potentials and regional cerebral blood flow equivalents during two- and three-sound auditory 'oddball tasks'. Electroencephalogr Clin Neurophysiol 1995;95:434–43.

Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 1999;125: 356–66.

Escera C, Alho K, Winkler I, Näätänen R. Neural mechanisms of involuntary attention to acoustic novelty and change. J Cogn Neurosci 1998;10:590–604.

Escera C, Alho K, Schröger E, Winkler I. Involuntary attention and distractibility as evaluated with event-related brain potentials. Audiol Neurootol 2000;5:151–66.

Frankenstein UN, Richter W, McIntyre MC, Rémy F. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. NeuroImage 2001;14:827–36.

Friederich M, Trippe RH, Özcan M, Weiss T, Hecht H, Miltner WHE. Laser-evoked potentials to noxious stimulation during hypnotic analgesia and distraction of attention suggest different brain mechanisms of pain control. Psychophysiology 2001;38:768–76.

Frot M, Mauguière F. Dual representation of pain in the operculo-insular cortex in humans. Brain 2003;126:438–50.

García-Larrea L, Peyron R, Laurent B, Mauguière F. Association and dissociation between laser-evoked potentials and pain perception. NeuroReport 1997;8:3785–9.

García-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin 2003;33:279–92.

Grillon C, Courchesne E, Ameli R, Elmasian R, Braff D. Effects of rare non-target stimuli on brain electrophysiological activity and performance. Int J Psychophysiol 1990;9:257–67.

Harmony T, Bernal J, Fernández T, Silva-Pereyra J, Fernández-Bouzas A, Marosi E, Rodríguez M, Reyes A. Primary task demands modulate P3a amplitude. Cogn Brain Res 2000;9:53–60.

Honoré J, Hénon H, Naveteur J. Influence of eye orientation on pain as a function of anxiety. Pain 1995;63:213–8.

Iannetti GD, Zambreanu L, Cruccu G, Tracey I. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience 2005;131:199–208.

Kakigi R, Shibasaki H, Ikeda A. Pain-related somatosensory evoked potentials following CO_2 laser stimulation in man. Electroencephalogr Clin Neurophysiol 1989;74:139–46.

Kakigi R, Hoshiyama M, Shimojo M, Naka D, Yamasaki H, Watanabe S, Xiang J, Maeda K, Lam K, Itomi K, Nakamura A. The somatosensory evoked magnetic fields. Prog Neurobiol 2000;61:495–523.

Kanda M, Fujiwara N, Xu X, Shindo K, Nagamine T, Ikeda A, Shibasaki H. Pain-related and cognitive components of somatosensory evoked potentials following CO_2 laser stimulation in man. Electroencephalogr Clin Neurophysiol 1996;100:105–14.

Kanda M, Nagamine T, Ikeda A, Ohara S, Kunieda T, Fujiwara N, Yazawa S, Sawamoto N, Matsumoto R, Taki W, Shibasaki H. Primary somatosensory cortex is actively involved in pain processing in human. Brain Res 2000;853:282–9.

Katayama J, Polich J. Stimulus context determines P3a and P3b. Psychophysiology 1998;35:23–33.

Kunde V, Treede RD. Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli. Electroencephalogr Clin Neurophysiol 1993;88: 280–9.

Legrain V, Guérit JM, Bruyer R, Plaghki L. Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. Pain 2002;99:21–39.

Legrain V, Bruyer R, Guérit JM, Plaghki L. Nociceptive processing in the human brain of infrequent task-relevant and task-irrelevant noxious stimuli. A study with event-related potentials evoked by CO_2 laser radiant heat stimuli. Pain 2003a;103:237–48.

Legrain V, Guérit JM, Bruyer R, Plaghki L. Electrophysiological correlates of attentional orientation in humans to strong intensity deviant nociceptive stimuli, inside and outside the focus of spatial attention. Neurosci Lett 2003b;339:107–10.

Lenz FA, Rios M, Zirh A, Chau D, Krauss G, Lesser RP. Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. J Neurophysiol 1998;79:2231–4.

Longe SE, Wise R, Bantick S, Lloyd D, Johansen-Berg H, McGlone F, Tracey I. Counter-stimulatory effects on pain perception and processing are significantly altered by attention: an fMRI study. NeuroReport 2001;12:2021–5.

Lorenz J, Bromm B. Event-related potential correlates of interference between cognitive performance and tonic experimental pain. Psychophysiology 1997;34:436–45.

Lorenz J, García-Larrea L. Contribution of attentional and cognitive factors to laser evoked brain potentials. Neurophysiol Clin 2003;33:293–301.

McCarthy G, Wood CC. Scalp distribution of event-related potentials: an ambiguity associated with analysis of variance models. Electroencephalogr Clin Neurophysiol 1985;64:203–8.

Mecklinger A, Opitz B, Friederici AD. Semantic aspects of novelty detection in humans. Neurosci Lett 1997;235:65–8.

Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. Pain 1989;39:345–52.

Näätänen R. Attention and brain function. Hillsdale, KS: Erlbaum; 1992.

Opsommer E, Guérit JM, Plaghki L. Exogenous and endogenous components of ultralate (C-fibre) evoked potentials following CO_2 laser stimuli to tiny skin surface areas in healthy subjects. Neurophysiol Clin 2003;33:78–85.

Pashler H, Johnston JC, Ruthruff E. Attention and performance. Annu Rev Psychol 2001;52:629–51.

Petrovic P, Peterson KM, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 2000;85:19–30.

Peyron R, García-Larrea L, Grégoire MC, Costes N, Convers P, Lavenne F, Mauguière F, Michel D, Laurent B. Haemodynamic brain responses to acute pain in humans. Sensory and attentional networks. Brain 1999; 122:1765–79.

Plaghki L. CO_2 laser stimulation. A modern way for exploring the somesthesic system and its usefulness for the study of the chronic pain state (unpublished doctoral thesis). Brussels: Université catholique de Louvain; 1997.

Plaghki L, Delisle D, Godfraind JM. Heterotopic nociceptive conditioning stimuli and mental task modulate differently the perception and physiological correlates of short CO_2 laser stimuli. Pain 1994;57: 181–92.

Rainville P. Brain mechanisms of pain affect and pain modulation. Curr Opin Neurobiol 2002;12:195–204.

Schlereth T, Baumgärtner U, Magerl W, Stoeter P, Treede RD. Left-hemisphere dominance in early nociceptive processing in the human parasylvian cortex. NeuroImage 2003;20:437–50.

Schröger E. On the detection of auditory deviations: a pre-attentive activation model. Psychophysiology 1997;34:245–57.

Schröger E, Wolff C. Behavioral and electrophysiological effects of task-irrelevant sound change: a new distraction paradigm. Cogn Brain Res 1998;7:71–87.

Siddle DAT. Orienting, habituation, and resource allocation: an associative analysis. Psychophysiology 1991;28:245–59.

Siedenberg R, Treede RD. Laser-evoked potentials: exogenous and endogenous components. Electroencephalogr Clin Neurophysiol 1996;100:240–9.

Spence C, Bentley DE, Philipps N, McGlone FP, Jones AKP. Selective attention to pain: a psychophysical investigation. Exp Brain Res 2002; 145:395–402.

Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 1975;38:387–401.

Tarkka IM, Treede RD. Equivalent electric source analysis of pain-related somatosensory evoked potentials by a CO_2 laser. J Clin Neurophysiol 1993;10:513–9.

Towell AD, Boyd SG. Sensory and cognitive components of the CO_2 laser evoked cerebral potential. Electroencephalogr Clin Neurophysiol 1993; 88:237–9.

Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueducal gray in humans. J Neurosci 2002;22:2748–52.

Valeriani M, Restuccia D, Barba C, Le Pera D, Tonali P, Mauguière F. Sources of cortical responses to painful CO_2 laser skin stimulation of the hand and foot in human brain. Clin Neurophysiol 2000;111: 1103–12.

Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fMRI analysis. Pain 2004;109:399–408.

Van Damme S, Crombez G, Eccleston C. Retarded disengagement from pain cues: the effects of pain catastrophizing and pain expectancy. Pain 2002;100:111–8.

Van Damme S, Crombez G, Eccleston C, Goubert L. Impaired disengagement from threatening cues of impending pain in crossmodal cueing paradigm. Eur J Pain 2004a;8:227–36.

Van Damme S, Lorenz J, Eccleston C, Koster EHW, De Clercq A, Crombez G. Fear-conditioned cues of impending pain facilitate attentional engagement. Neurophysiol Clin 2004b;34:33–9.

Vogel H, Port JD, Lenz FA, Solaiyappan M, Krauss G, Treede RD. Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. J Neurophysiol 2003;89:3051–60.

Williams LM, Brammer MJ, Skerrett D, Lagopoulos J, Rennie C, Kozek K, Olivieri G, Peduto T, Gordon E. The neural correlates of orienting: an integration of fMRI and skin conductance orienting. NeuroReport 2000; 11:3011–5.

Woods DL. Auditory selective attention in middle-aged and elderly subjects: an event-related brain potential study. Electroencephalogr Clin Neurophysiol 1992;84:456–68.

Yago E, Escera C, Alho K, Giard MH, Serra-Grabulosa JM. Spatiotemporal dynamics of the auditory novelty-P3 event-related brain potential. Cogn Brain Res 2003;16:383–90.

Yamasaki H, Kakigi R, Watanabe S, Naka D. Effects of distraction on pain perception: magneto- and electro-encephalographic studies. Cogn Brain Res 1999;8:73–6.

Zaslansky R, Sprecher E, Tenke CE, Hemli JA, Yarnitsky D. The P300 in pain evoked potentials. Pain 1996;66:39–49.