



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

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Abstract

Laser evoked potentials (LEPs) are brain responses to activation of skin nociceptors by laser heat stimuli. LEPs consist of three components: N1, N2, and P2. Previous reports have suggested that in contrast to earlier activities (N1), LEPs responses after 230–250 ms (N2–P2) are modulated by attention to painful laser stimuli. However, the experimental paradigms used were not designed to specify the attentional processes involved in these LEP modulations. We investigated the effects of selective spatial attention and oddball tasks on LEPs. CO₂ laser stimuli of two different intensities were delivered on the dorsum of both hands of ten subjects. One intensity was frequently presented, and the other rarely. Subjects were asked to pay attention to stimuli delivered on one hand and to count rare stimuli, while ignoring stimuli on the other hand. Frequent and rare attended stimuli evoked enhanced N160 (N1) and N230 (N2) components in comparison to LEPs from unattended stimuli. Both components showed scalp distribution contralateral to the stimulus location. The vertex P400 (P2) was unaffected by spatial attention and stimulus location, but its amplitude increased after rare stimuli, whether attended or unattended. An additional parietal P600 component was induced by the attended rare stimuli. It is suggested that several attentional processes can modify nociceptive processing in the brain at different stages. LEP activities in the time-range of N1 and N2 (120–270 ms) showed evidence of processes modulated by the direction of spatial attention. Conversely, processes underlying P2 (400 ms) were not affected by spatial attention, but by the probability of the stimulus. This probability effect was not due to P3b-related processes that were observed at a later latency (600 ms). Indeed, P600 could be seen as a P3b evoked by conscious detection of rare targets. © 2002 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Event-related potentials (ERPs) are electrical responses of the brain to external or internal events. Because of their good temporal resolution, ERPs are widely used to study the sequence of operations triggered in the human brain in perception, attention, memory or language. Laser evoked potentials (LEPs), introduced by Carmon et al. (1976), are nociceptive-related brain potentials evoked by radiant heat stimulation of the skin by lasers such as the CO₂ laser. This technique (1) allows to activate specifically nociceptors related to A δ and C fibers, (2) without any skin contact,

and (3) with a sharp rise of skin surface temperature eliciting synchronous afferent discharges enabling the recording of evoked brain potentials (Meyer et al., 1976; Bromm and Treede, 1984; Plaghki, 1997). Therefore, LEPs provide a useful tool to study the sequence of brain processes involved in nociception, thus allowing a better understanding of pain perception. However, up to now, only a few studies attempted to link the different LEP components to precise nociceptive brain processes. LEPs elicited by A δ -fibers activations are mainly composed of two components, N2 and P2 peaking, respectively, at about 200–250 and 350–400 ms after hand stimulation, with a maximal amplitude at the vertex (Treede et al., 1988; Kunde and Treede, 1993; Miyazaki et al., 1994; Spiegel et al., 1996). Source localization studies suggest that dipoles located in the bilateral parasyll-

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vian areas (SII, insula) and the anterior cingulate gyrus (ACG) could explain N2, while P2 would be mainly explained by an ACG dipole (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996). Bilateral SII activation to noxious stimuli was confirmed by magnetoencephalography (MEG) (Kakigi et al., 1995; Laudhan et al., 1995; Watanabe et al., 1998; Ploner et al., 1999; Kanda et al., 2000), intracortical LEP recordings (Frot et al., 1999), and neuroimaging studies (see Peyron et al., 2000). ACG activation was not clearly demonstrated by MEG studies (Laudhan et al., 1995; Watanabe et al., 1998; Yamasaki et al., 1999) but it was by subdural recordings (Lenz et al., 1998b) and PET/fMRI studies (see Peyron et al., 2000). Finally, N2 may be preceded by N1 that appears as a small shoulder in the N2 ascending slope (Treede et al., 1988). N1 was better observed after strong stimuli, at the contralateral midtemporal leads, and often with a frontal or nose reference (Treede et al., 1988; Kunde and Treede, 1993; Miyazaki et al., 1994; Spiegel et al., 1996; Valeriani et al., 1996). N1 is suggested to originate from the contralateral SII (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996) and maybe SI areas (Tarkka and Treede, 1993; Ploner et al., 1999; Kanda et al., 2000). Although N2 and P2 are necessarily evoked by laser stimuli, they are nevertheless modulated by both extrinsic (e.g. intensity) and intrinsic (e.g. attention) factors depending on the subjects state and the experimental context.

1.1. LEPs and attentional modulation

Several studies have shown that the amplitude of the LEPs can be modulated by attention (Beydoun et al., 1993; Zaslansky et al., 1996; García-Larrea et al., 1997; Yamasaki et al., 1999). These studies used “attention vs. distraction” tasks in which subjects were asked to orient their attention toward either laser-induced nociceptive stimuli (attention) or to other types of stimuli (distraction). It was found that N2–P2 amplitudes were enhanced in the attentive condition as compared to the distractive condition, whereas the N1 amplitude was unaffected. Results were sometimes interpreted in terms of selective attention (Beydoun et al., 1993; García-Larrea et al., 1997), which is understood as mechanisms that control the flow of afferent information in order to select and process relevant inputs and to avoid interference of irrelevant inputs. Most theories of selective attention are based on the assumption of a limited processing capacity of the brain, and of a priority of processing in order to avoid informational overload (for a critical review see Allport, 1989). ERP experiments studied selective attention by means of a sustained attention task (see Hillyard et al., 1995), in which subjects are shown two or more series of stimuli delivered randomly, each series referring to a *channel*, i.e. a category of stimuli sharing the same feature (Broadbent, 1958) such as location, pitch of tones, or color. In such designs, subjects are instructed to pay attention to the stimuli belonging to a

specific channel, and to ignore the others. Differences in the ERP parameters between the attended (the relevant channel) and the unattended stimuli (another channel) were observed at early latencies (see Näätänen, 1992; Hillyard et al., 1995). It suggests that the attended and unattended stimuli are processed differently by the brain and at an early processing stage, that is, before the generation of a perceptual representation of the stimulus (see Broadbent, 1958; Posner, 1980). The earlier effects were found between 80 and 100 ms after stimulus onset for visual ERPs (Hillyard and Münte, 1984; Mangun and Hillyard, 1988, 1990; Heinze et al., 1990; Mangun et al., 1993), between 20 and 50 ms for auditory ERPs (Woldorff and Hillyard, 1991), and between 30 and 40 ms for electrical somatosensory ERPs (Josiassen et al., 1982; Desmedt et al., 1983; Desmedt and Tomberg, 1989). These selective attention-modulated brain responses were suggested to originate from sensory specific cortical areas. Two main propositions were made to explain selective attention effects on the ERPs. Firstly, according to the *sensory gain control* hypothesis, the flow of information is efferently gated in cortical areas, in such a way that the processing of the attended stimuli is facilitated in comparison to unattended stimuli (Hillyard et al., 1995). Secondly, the *attentional trace* hypothesis proposed that the inputs are compared to a template of the relevant feature encoded in memory: inputs matching the template are further processed, while inputs mismatching the template are fully or partially rejected from higher-order processing (Näätänen, 1992).

In the previous studies (Beydoun et al., 1993; Zaslansky et al., 1996; García-Larrea et al., 1997; Yamasaki et al., 1999), LEPs were recorded in the attentive condition without any concurrent stimuli. Therefore, LEP amplitudes may not index selective attention facilitation. At least, it remains plausible that smaller amplitudes in the distractive conditions would be due to suppression of the laser-evoked brain responses. Nevertheless, LEPs were compared when subjects were involved in different tasks varying in nature and complexity, providing no control over arousal level between the different conditions. As a result, these studies were not properly designed to dissociate specific stimulus selective processing from non-specific variations of arousal.

1.2. LEP and P300 components

Another difficulty with previous reports is that laser stimuli in the attentive conditions had to be detected by mental counting or button-pressing. These stimuli could then be seen as targets leading to an overlap of a P3b-like component in the P2 time-range. The P3b component, observed in all modalities, is usually evoked in the oddball paradigm by rare stimuli interspersed into frequent stimuli, when subjects are actively involved in the detection of rare stimuli. P3b displays a parietal distribution and is suspected of reflecting the updating of working memory (Donchin and Coles, 1988) or the closure of contextual processing

(Desmedt, 1980; Verleger, 1988). P3b could also be obtained in a one-stimulus paradigm in which stimuli are rarely presented without any standard stimuli (as if the frequent stimuli were absent) and subjects are instructed to detect all stimuli (e.g. Polich et al., 1994). Using very large interstimulus intervals (6–10 s), the attentive conditions of Beydoun et al. (1993), García-Larrea et al. (1997) and Zaslansky et al. (1996) could be readily seen as similar to a one-stimulus oddball condition, with rare laser stimuli among silence and leading to P3b elicitation. Zaslansky et al. (1996) claimed that the laser-evoked P2 could be considered as a P3b-like component. However, the parietal P3b was observed later than P2 at about 600 ms in LEP studies using the classical two-stimulus oddball paradigm (Towell and Boyd, 1993; Kanda et al., 1996; Siedenberg and Treede, 1996; Plaghki, 1997). It is worth noting that, in addition to the P3b, there are other kinds of P300 components reflecting different processes and generated in different brain areas. For example, the P3a component, suggested to reflect an orientation response, is elicited by rare deviant or novel¹ events, even when they are task-irrelevant or unexpected (Courchesne et al., 1975; Squires et al., 1975; Yamaguchi and Knight, 1991; Escera et al., 1998; Katayama and Polich, 1998). Even if most previous reports concluded that P2 does not correspond to the P3b, the question remains open with respect to other kinds of P300 components that could be held responsible for the attentional modulation of the LEPs.

The goals of the present study are (1) to evidence an effect of selective spatial attention on LEPs in a sustained attention paradigm, where attention was focused on a given hand while both hands were stimulated during the same task, thus providing control over the level of arousal, and (2) to dissociate this effect from an *oddball* effect due to the detection of rare targets among frequent stimuli.

2. Methods

2.1. Subjects

LEPs were recorded in ten right-handed healthy subjects (five men, five women, 26.2 ± 3.6 years old) who gave informed consent and were free of any neurological, psychiatric, and chronic pain disorder. The subjects took part in the experiment in two different sessions separated by at least 5 days and lasting about 2.5 h each.

2.2. Stimuli

Cutaneous heat stimuli were delivered by a CO₂ laser (10.6 μm wavelength) on the dorsum of both hands. The laser was designed and built in the Department of Physics

(Université catholique de Louvain, Belgium). A He–Ne laser beam coaxial to the infrared beam visualized stimulus impact. Stimulus duration was 50 ms and its surface area was 80 mm². In order to minimize habituation or nociceptors sensitization, the laser beam was slightly moved between each stimulus. Beam impact shifted from one hand to the other by means of a remotely controlled two-position flat mirror. Distance between beam impacts on each hand was constant. Both hands were placed at the same distance from the last mirror of the optical guidance system. Two energy levels were used: 550 mJ defining a *weak intensity* and 750 mJ defining a *strong intensity*. Because of the thermal drift of the laser equipment, the two energy levels increased by about 7% at the end of the session as compared to the initial value. However, the difference between the two energy levels did not change between the beginning and the end of the first ($t = -2.20$, $P = 0.055$) and the second experimental session ($t = -1.53$, $P = 0.160$). In addition, the difference in energy levels was the same between the two sessions, before ($t = 0.48$, $P = 0.643$) and after ($t = 0.69$, $P = 0.504$) EEG recording.

2.3. Procedure

Subjects were seated on a chair, with the forearms placed on a table, in an air-conditioned room (22–24°C). To avoid any visual clue, instruments were hidden from subject's view by a wooden board with a hole through which the hands and the forearms were extended. To avoid acoustic clues, background noise was diffused through earphones. During the first session, a first set of stimuli of increasing intensity was presented in order to make the subjects familiar with the laser stimuli. A second set with the two experimental energy levels was then presented to the subjects to allow them to discriminate between both levels. Both stimuli were perceived as a painful pinprick. Subjects were then exposed to 16 blocks of stimuli per session (32 blocks in total). Each block consisted of 50 stimuli with a constant 3 s interstimulus interval (ISI). The stimuli were delivered randomly on each hand with the same probability (50% on the right hand, 50% on the left hand). On each hand, both intensities were presented under different probabilities: one intensity was frequent (80%), the other was rare (20%). One block thus consisted of 25 stimuli on the right hand, 20 frequent and five rare, and 25 stimuli on the left hand, 20 frequent and five rare. For 16 of the 32 blocks, frequent stimuli were of weak intensity and rare of strong intensity. For the remaining 16, probabilities of stimulus intensities were reversed. The order of stimuli was pseudo-random with the restriction that a rare stimulus was always preceded by a frequent stimulus on the same hand.

Subjects were instructed (1) to maintain their gaze on a central fixation point, (2) to pay attention to stimuli delivered on a given hand, (3) to count the rare stimuli on that hand, (4) to ignore all what happened on the other hand, and

¹ The novel stimuli are series of different complex and unique stimuli such as natural sounds, or color or form patterns, interspersed among frequent and target stimuli, and presented only once or a very few times during the entire experiment.

(5) to report at the end of each block the number of rare stimuli. The 32 blocks were split among four tasks (eight blocks per task, four per session): I. To attend to the right hand and to count rare strong stimuli; II To attend to the right hand and to count rare weak stimuli; III To attend to the left hand and to count rare strong stimuli; IV. To attend to the left hand and to count rare weak stimuli. The order of conditions was randomly assigned to each subject for the first session. During the second session, the reverse order was used. Each session began with a non-recorded block of the first task. The four kinds of stimuli (right vs. left, strong vs. weak) were presented in four conditions (attended vs. unattended, frequent vs. rare). Only the attended rare stimuli were to be counted.

2.4. Recording

LEPs were recorded by 19 Ag–AgCl electrodes placed on the scalp according to the International 10–20 System: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, O2 referenced to linked earlobes. Impedance was kept below 5 k Ω . Ground was placed at the right wrist. Ocular movements and eye blinks were monitored by electro-oculography (EOG) recorded from two electrodes, one at the upper left and the other at the lower right side of the right eye. EEG was recorded by a PL-EEG device (Walter Graphtek, Germany): sample rate 167 cps, time constant 3 s, gain 1000, filters 0.06–75 Hz, notch filter 50 Hz. Data were stored on hard disk for off-line analysis (Scan 3.0, Neuroscan, USA). The analysis time window extended from 500 ms before to 2566 ms after stimulus onset (512 points). Sweeps were digitally filtered with a band pass of 0.3–20 Hz (24 dB/octave) and baseline corrected to the –500 to 0 ms time interval. Artifacted sweeps i.e. EOG-contaminated sweeps and sweeps containing activity exceeding 80 μ V, were rejected by visual inspection. Artifact-free sweeps were averaged according to the conditions whatever the stimulus intensity, yielding eight different averaged LEPs per subject: 2 locations (R-HAND vs. L-HAND) \times 2 attention conditions (ATT vs. UNATT) \times 2 probabilities (FREQ vs. RARE).

2.5. Data analysis

Performance assessment was based on percentage of errors. For technical reasons, a motor response could not be made. Consequently, no reaction time was recorded, and misses and false alarms could not therefore be detected. This implies that behavioral scores are approximations of the actual performance of the subjects. Because EEG sweeps evoked by the two intensities in each condition were pooled before averaging, two different scores were also computed, one for paying attention to the right hand and another for paying attention to the left hand.

LEP components were identified as follows. P2 was first defined at Cz as the positive component with a maximal amplitude between 350 and 450 ms. N2 was then defined

as the negative component preceding P2 between 200 and 270 ms. N2 was identified at Cz, but also at contralateral electrodes (C3 and T3 for R-HAND stimuli, C4 and T4 for L-HAND stimuli). N1 was then defined as the negative component preceding N2 between 120 and 200 ms, and identified at contralateral electrodes. A fourth component with positive polarity, was looked at Pz after P2 between 550 and 650 ms in the ATT RARE condition, and was then looked for in the other conditions. Once identified at the above-mentioned electrodes, the four LEP components were searched for on the other electrodes by traces superposition. Cz, Pz, Fz, C3, C4, T3, and T4 electrodes were used for analysis. Latencies were measured from stimulus onset to peak. Amplitudes were measured from peak to the 500-ms pre-stimulus baseline.

LEP amplitudes and latencies were submitted to four-factors analyses of variance (ANOVA) with repeated measures (2 locations \times 2 attention conditions \times 2 probabilities \times 7 electrodes) with correction of the degrees of freedom by the Greenhouse-Geisser method and contrasts analysis of means. Performance was analyzed by the Wilcoxon test. Significance level was set at $P < 0.05$.

To assess LEP topographical distributions across conditions, amplitudes were re-analyzed after normalization. This analysis was intended for circumventing the fundamental incompatibility between the additive ANOVA model and the multiplicative effect on evoked potential voltages produced by changes in source strength (McCarthy and Wood, 1985). For each condition, each subject's amplitude was divided by the square root of the sum of the squared mean amplitudes from each of the seven electrodes. This method normalized the effects of location, attention, and probability conditions.

3. Results

Subjects detected 6.4 ± 1 targets per block on the right hand and 6.6 ± 1.3 targets on the left hand. Percentages of errors were 8.8 ± 3.7 and $8.6 \pm 3.8\%$, respectively. The difference was not significant ($z = -0.20$, $P = 0.838$).

Figs. 1 and 2 show grand-mean LEPs across T3–C3–Cz–C4–T4, and Figs. 3 and 4 across Fz–Cz–Pz, for R-HAND and L-HAND, respectively. LEPs were composed of a broad negativity followed by a still broader positivity. The negativity consisted of two components. The first one appeared at a mean peak latency of 160 ms (N160), while the second was observed at a 230 ms peak latency (N230). These two components were well segregated in eight out of the ten subjects (Fig. 5). In the two remaining subjects, N160 was not evidenced in all conditions. Both components displayed greater amplitudes in the ATT than in the UNATT condition with maximal amplitude at contralateral electrodes. The largest positive component was peaking at about 400 ms with maximal amplitude at Cz (P400). A second positive component appeared at about 600 ms and was

clearly identified in the ATT RARE condition with a maximum amplitude at Pz (P600). In the other conditions, P600 appeared more as a shoulder in the P400 slope when return-

ing to baseline. Fig. 6 shows a topography contralateral to the stimulus location for activities in the time range of the N160–N230 complex. Fig. 7 shows maps in the time range

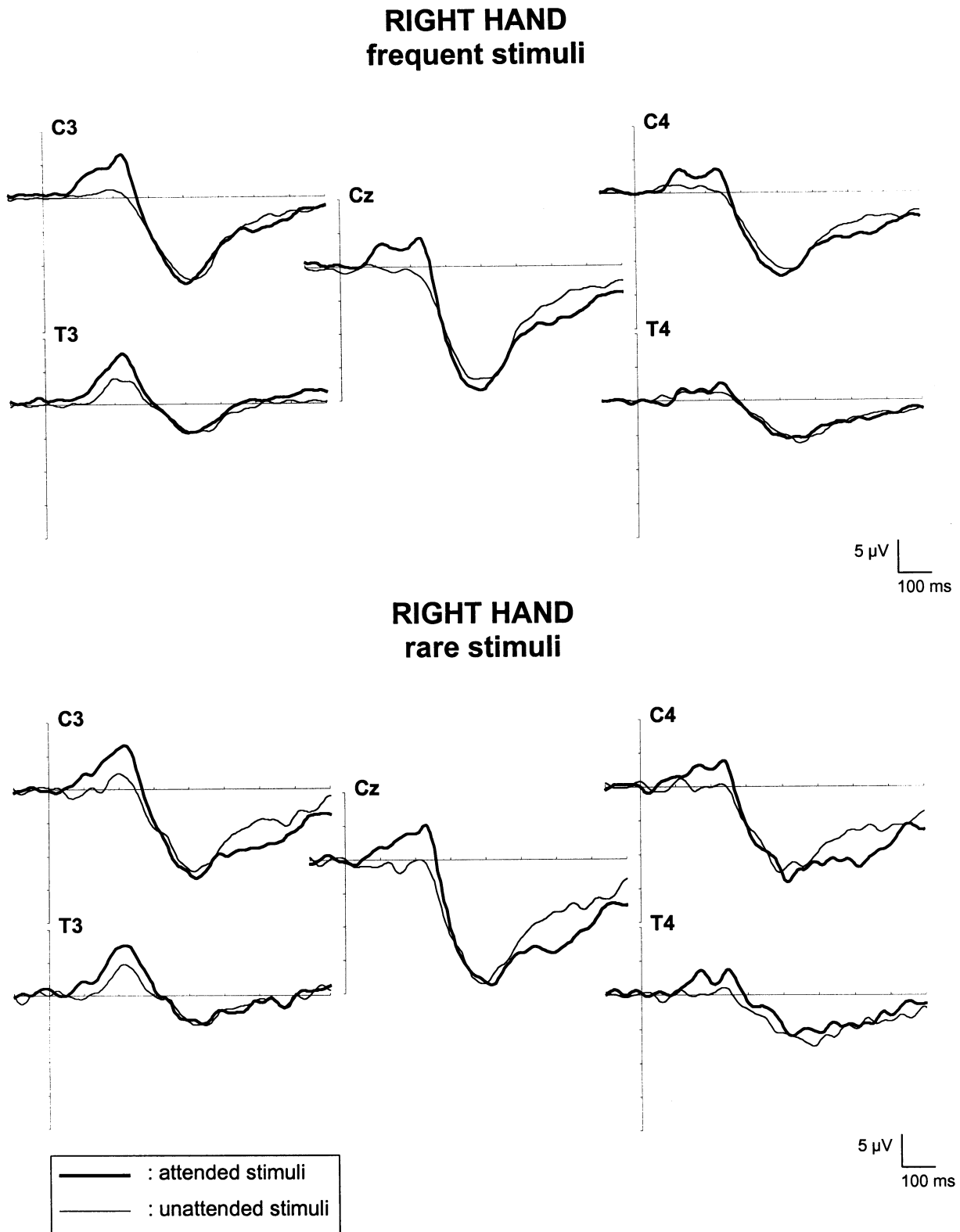


Fig. 1. Grand-mean LEPs for attended (thick line) and unattended (thin line) stimuli to the right hand in the frequent (above) and rare (below) conditions.

of the P400–P600 complex with a central peak activity between 350 and 500 ms becoming more posterior after 550 ms, mainly in the ATT RARE condition.

3.1. Amplitudes

Main effects and interactions of ANOVA on LEP ampli-

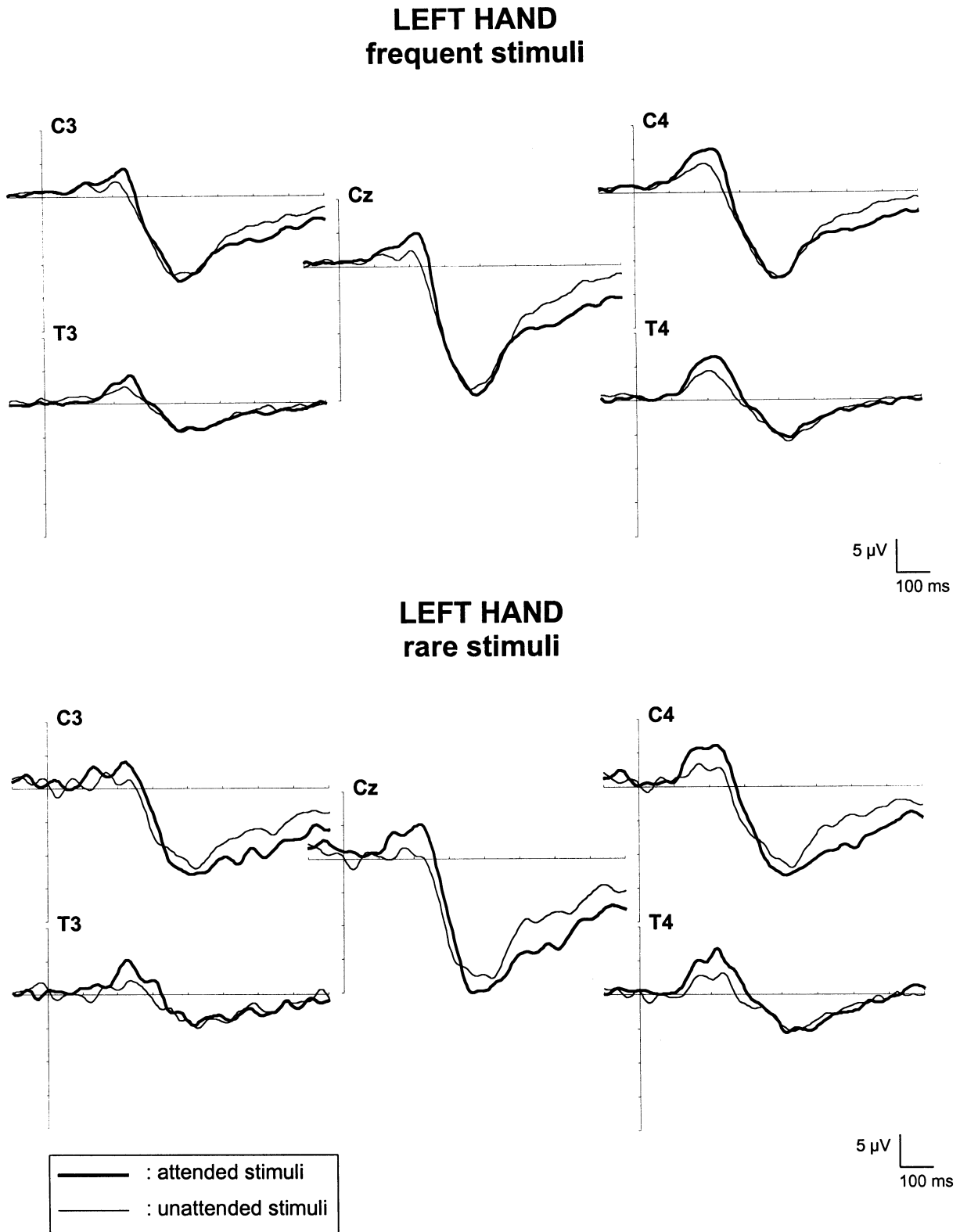


Fig. 2. Grand-mean LEPs for attended (thick line) and unattended (thin line) stimuli to the left hand in the frequent (above) and rare (below) conditions.

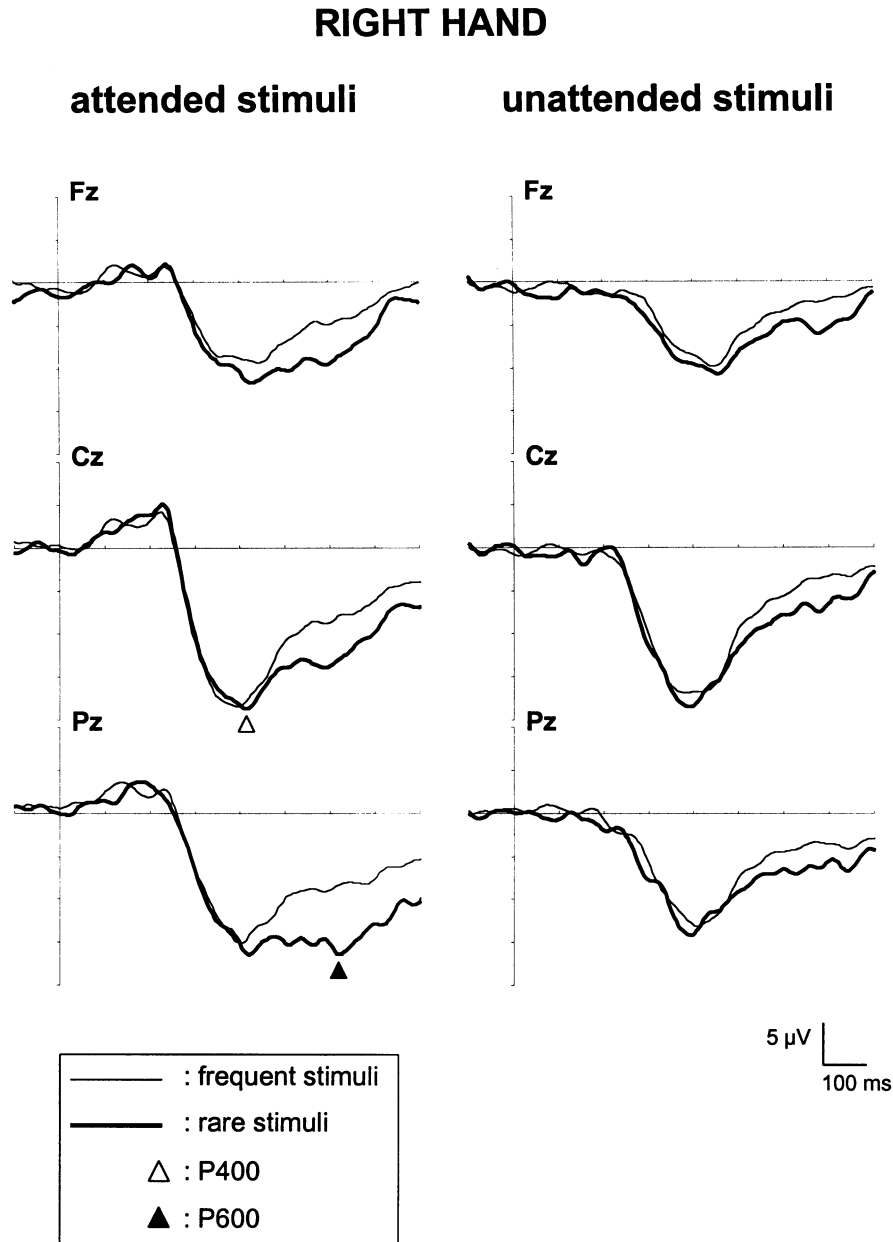


Fig. 3. Grand-mean LEPs for rare (thick line) and frequent (thin line) stimuli to the right hand in the attended (left part) and unattended (right part) conditions.

tudes are presented in Table 1. For each of the four identified components, the main effects are presented first, followed by the significant interactions between factors. Contrast analysis is used when appropriate.

The N160 amplitude was larger in the ATT than in the UNATT condition. It was maximum at contralateral electrodes (Fig. 8). When R-HAND was stimulated, N160 amplitude was larger at C3 than at C4 ($F_{1,7} = 13.85$, $P = 0.009$) and at T3 than at T4 ($F_{1,7} = 24.51$, $P = 0.002$). For L-HAND stimuli, N160 amplitude was larger at C4 ($F_{1,7} = 38.42$, $P < 0.001$) and T4 ($F_{1,7} = 52.17$, $P < 0.001$) than at C3 and T3, respectively. This contralateral topography was systematically observed in the ATT condition. In contrast, in the UNATT condition,

the difference between C3 and C4 for R-HAND condition was no longer significant ($F_{1,7} = 1.93$, $P = 0.172$).

For N230, attentional effect and contralateral topography were observed as for N160 (Fig. 8). For R-HAND stimulation, N230 amplitude was larger at C3 than at C4 ($F_{1,9} = 22.00$, $P = 0.001$) and at T3 than at T4 ($F_{1,9} = 74.01$, $P < 0.001$). The reverse was observed for L-HAND stimulation for C3–C4 ($F_{1,9} = 39.85$, $P < 0.001$) and T3–T4 comparisons ($F_{1,9} = 39.61$, $P < 0.001$). Additionally, N230 amplitude at Cz was higher than at ipsilateral electrodes in the ATT condition (R-HAND: $F_{1,9} = 3.88$, $P = 0.054$ [Cz–C4 comparison], $F_{1,9} = 11.95$, $P = 0.007$ [Cz–T4]; L-HAND: $F_{1,9} = 12.82$, $P < 0.001$ [Cz–C3], $F_{1,9} = 16.73$, $P < 0.001$ [Cz–T3]),

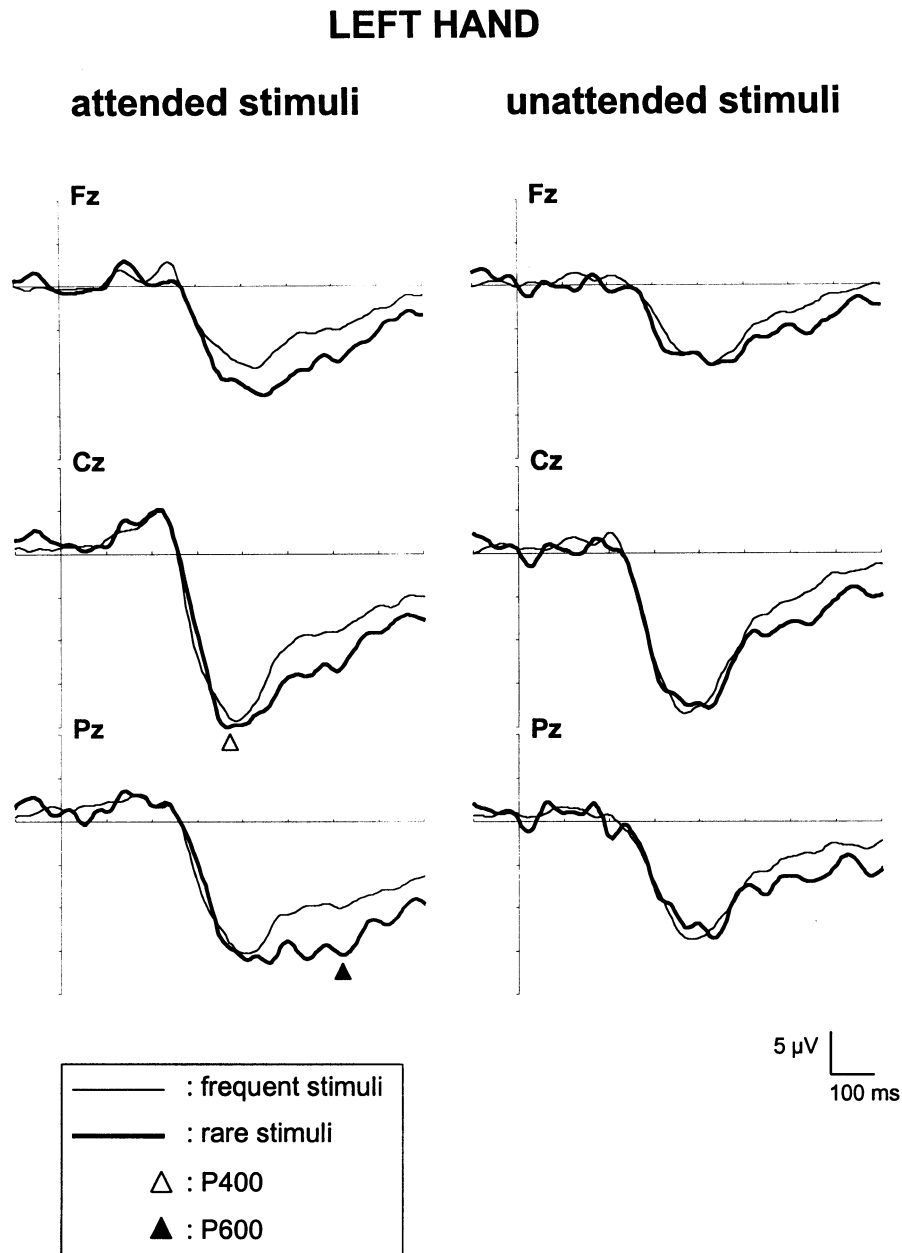


Fig. 4. Grand-mean LEPs for rare (thick line) and frequent (thin line) stimuli to the left hand in the attended (left part) and unattended (right part) conditions.

while no significant difference emerged in the UNATT condition (R-HAND: $F_{1,9} = 1.80$, $P = 0.177$ [Cz–C4], $F_{1,9} = 2.42$, $P = 0.134$ [Cz–T4]; L-HAND: $F_{1,9} = 0.09$, $P = 0.593$ [Cz–C3], $F_{1,9} = 1.53$, $P = 0.201$ [Cz–T3]).

P400 amplitude was maximal at Cz in all conditions (Fig. 9) and was enhanced by RARE stimuli. ATT RARE stimuli evoked larger P400 amplitude than ATT FREQ ($F_{1,9} = 15.32$, $P = 0.004$), and UNATT RARE stimuli elicited a larger amplitude than UNATT FREQ stimuli ($F_{1,9} = 9.80$, $P = 0.012$). P400 amplitude was also greater for ATT RARE stimuli compared to UNATT FREQ stimuli ($F_{1,9} = 25.77$, $P < 0.001$). There was no attention effect,

except at Pz where amplitude was greater for ATT than UNATT stimuli ($F_{1,9} = 21.70$, $P = 0.002$).

P600 amplitude was larger in the ATT RARE than in the ATT FREQ ($F_{1,9} = 70.32$, $P < 0.001$), UNATT FREQ ($F_{1,9} = 133.81$, $P < 0.001$) and UNATT RARE conditions ($F_{1,9} = 50.81$, $P < 0.001$) (Fig. 9). Amplitude was lower in the UNATT FREQ condition than in the ATT FREQ ($F_{1,9} = 10.12$, $P = 0.011$) and UNATT RARE conditions ($F_{1,9} = 19.71$, $P = 0.002$). The ATT FREQ and UNATT RARE conditions did not differ from each other ($F_{1,9} = 1.58$, $P = 0.240$), except at Fz where P600 amplitude was larger for UNATT RARE stimuli ($F_{1,9} = 5.48$,

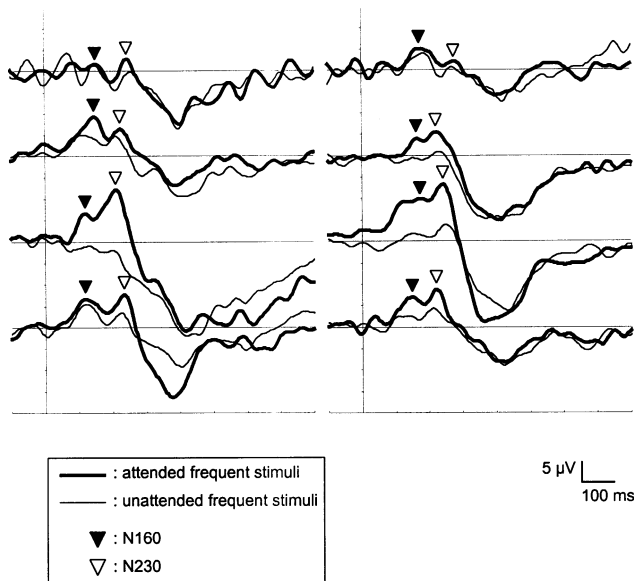


Fig. 5. Illustration of the N160 (black triangle) and N230 (white triangle) components at C3 in eight subjects following frequent stimuli to the left hand.

$P = 0.039$). P600 topography changed between conditions: its amplitude was larger at Pz than at Cz in the ATT RARE condition ($F_{1,9} = 59.57$, $P < 0.001$), and at Cz than at Pz in the UNATT FREQ condition ($F_{1,9} = 5.84$, $P = 0.034$), while there was no significant difference between Cz and Pz in the ATT FREQ ($F_{1,9} = 0.73$, $P = 0.338$) and UNATT RARE conditions ($F_{1,9} = 1.93$, $P = 0.170$). Finally, amplitude was larger at ipsilateral central electrodes: R-HAND stimuli evoked larger P600 amplitude at C4 than at C3 ($F_{1,9} = 16.89$, $P = 0.003$), while L-HAND stimuli evoked a larger amplitude at C3 than at C4 ($F_{1,9} = 10.37$, $P = 0.012$).

3.2. Normalized amplitudes

For each condition, each subject's amplitude was divided by the square root of the sum of the squared mean amplitudes from each of the seven electrodes (see Section 2.5). Analysis of normalized amplitudes confirmed the contralateral topography of N160² ($F_{6,42} = 10.56$, $P = 0.001$) and N230 ($F_{3,28} = 13.46$, $P < 0.001$). The topography of N230, but not N160, was significantly modulated by attention ($F_{4,31} = 3.76$, $P = 0.016$). Amplitude at Cz was not different from amplitudes at contralateral electrodes in the ATT condition, while it was lower in the UNATT condition (R-HAND: $F_{1,9} = 19.87$, $P = 0.001$ [Cz–C3]; $F_{1,9} = 81.05$, $P < 0.001$ [Cz–T3]; L-HAND: $F_{1,9} = 15.56$, $P < 0.001$ [Cz–C4], $F_{1,9} = 15.98$, $P < 0.001$ [Cz–T4]). Thus, N230 did display a contralateral topography in ATT and in UNATT condi-

² The contralateral topography of N160 was significant for all comparisons including C3 vs. C4 in the R-HAND UNATT condition ($F_{1,9} = 6.46$, $P = 0.046$).

tions, but the difference between both conditions appeared only at Cz (Fig. 10).

The normalized amplitude of P400 displayed only a significant main effect of electrodes ($F_{6,54} = 51.28$, $P < 0.001$) showing that P400 amplitude was maximal at Cz across all conditions. The analysis of normalized P600 amplitude confirmed that P600 was larger at Pz for ATT RARE condition ($F_{1,9} = 26.48$, $P < 0.001$) and at Cz for UNATT FREQ condition ($F_{1,9} = 13.38$, $P = 0.005$), while there was no significant difference between Cz and Pz in the ATT FREQ ($F_{1,9} = 0.88$, $P = 0.289$) and UNATT RARE conditions ($F_{1,9} = 1.95$, $P = 0.165$) (Fig. 11). Difference between central ipsilateral and contralateral electrodes was still significant.

3.3. Latencies

Table 2 displays the results of the four-factors ANOVA for LEP latencies. There was no significant effect or interaction for N160 and P600 latencies. N230 latencies were shorter for the FREQ than for the RARE stimuli. They were longer at Fz and Pz electrodes. P400 latencies were shorter at Cz, except for ATT FREQ and UNATT RARE conditions where the difference was not significant relative to Pz. P400 latencies were longer at T3 and T4 electrodes than at all other electrodes. They were shorter in the ATT FREQ than in the ATT RARE ($F_{1,9} = 21.58$, $P = 0.001$) and UNATT RARE ($F_{1,9} = 9.69$, $P = 0.013$) conditions, but not significantly shorter than in the UNATT FREQ condition ($F_{1,9} = 4.65$, $P = 0.058$).

4. Discussion

In a selective spatial attention paradigm involving a target-detection task, brain potentials evoked by CO₂ laser heat stimuli, presented on both hands at random, elicited four main components: N160, N230, P400, and P600. The first three components seem to correspond rather well to the previously labeled N1, N2, and P2. The P600 component had a larger amplitude and a parietal distribution for the attended, rare, and to-be-counted stimuli.

4.1. The negativities N160 and N230

N160 and N230 peak amplitudes were larger for stimuli delivered to the attended hand relative to stimuli to the same hand when attention was focused on the other hand. Amplitudes of the negativities between attended frequent and attended rare stimuli were very similar. Their scalp distribution was specific to the stimulated hand. Similar effects have been demonstrated in other sensory modalities with the same kind of paradigm. Visual ERP studies indicated amplitude enhancement as early as the occipital P1 (starting from 80 to 90 ms) when attention was focused on the stimulus location (Hillyard and Münte, 1984; Mangun and Hillyard, 1988, 1990; Heinze et al., 1990; Mangun et al., 1993).

Because spatial attention-related P1 effect occurred without any change in latency, topography, wave form, and dipole location, it was suggested that spatial attention modifies the

sensory-evoked activity within the extrastriate cortex (Mangun et al., 1993; Gomez Gonzalez et al., 1994; Clark and Hillyard, 1996), supporting the gain control hypothesis

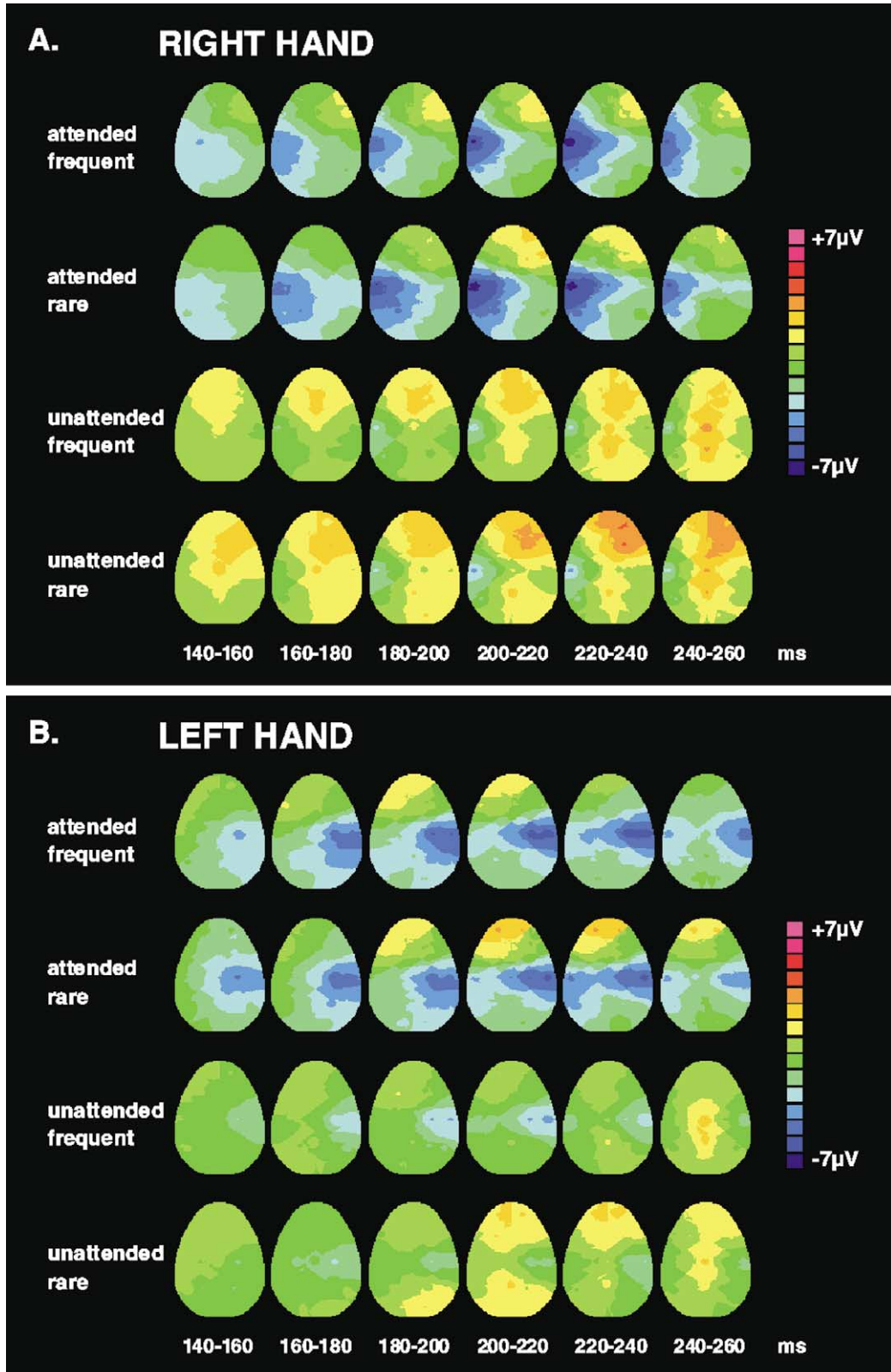


Fig. 6. Dynamic topographical maps of LEP negativities between 140 and 260 ms (top views).

(Hillyard et al., 1995). The selective attention effect on the auditory ERPs appeared from 80 ms (Nd components) (Hillyard et al., 1973; Schwent et al., 1976a,b; Hansen and Hill-

yard, 1980, 1984; Alho et al., 1987a,b) or even earlier (Woldorff and Hillyard, 1991). The earliest somatosensory effects were found at about 30–40 ms (Josiassen et al., 1982;

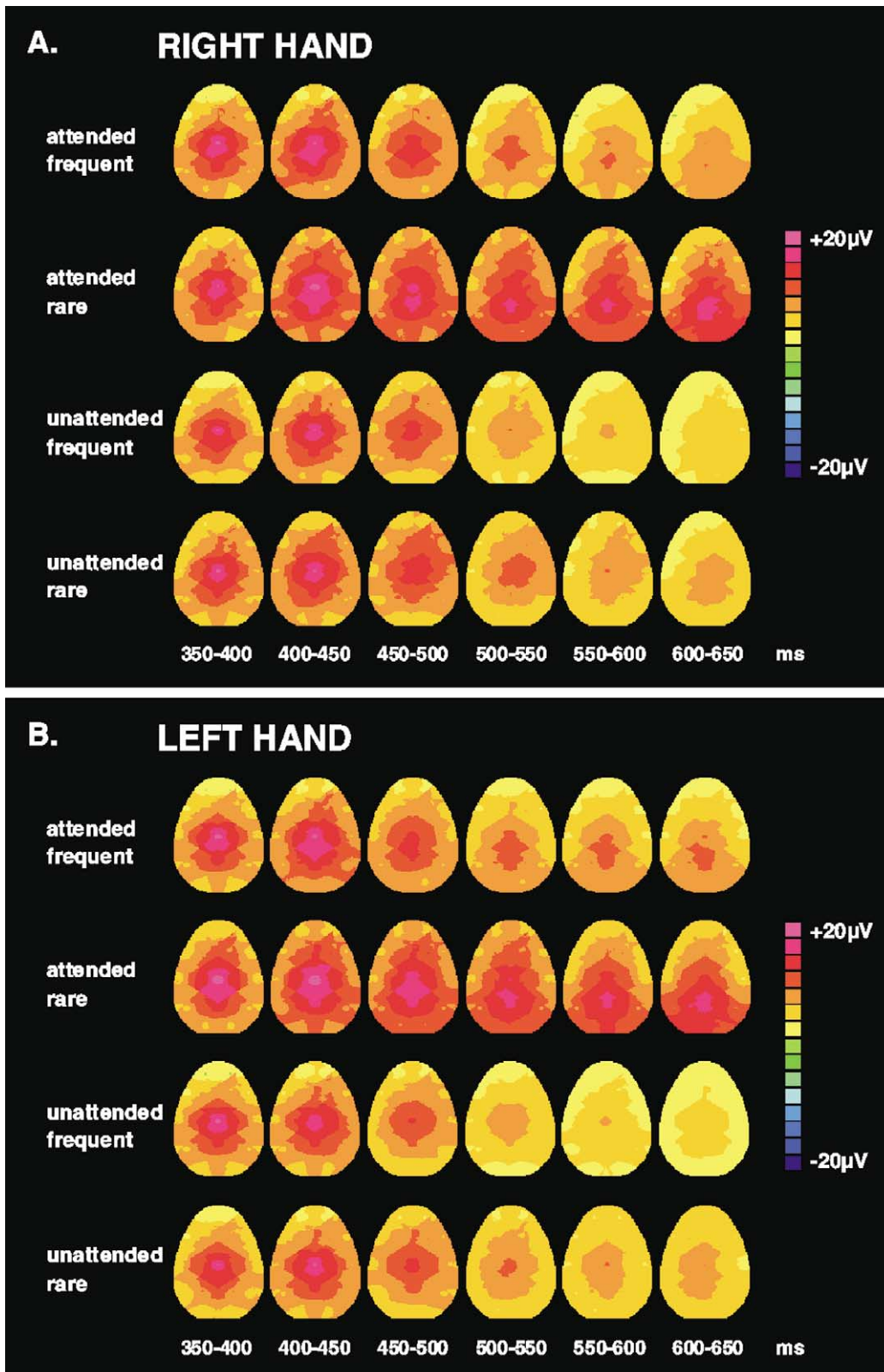


Fig. 7. Dynamic topographical maps of LEP positivities between 350 and 650 ms (top views).

Table 1
ANOVA for LEP amplitudes^a

Factors and interactions	N160 ^b			N230 ^c			P400 ^c			P600 ^c		
	d.f.	<i>F</i>	<i>P</i>	d.f.	<i>F</i>	<i>P</i>	d.f.	<i>F</i>	<i>P</i>	d.f.	<i>F</i>	<i>P</i>
Location	1,7	1.18	0.313	1,9	2.90	0.123	1,9	1.77	0.216	1,9	0.18	0.679
Attention	1,7	29.45	0.002***	1,9	64.32	0.000***	1,9	2.22	0.171	1,9	21.20	0.001***
Probability	1,7	1.95	0.205	1,9	0.55	0.477	1,9	6.93	0.027*	1,9	76.78	0.000***
Electrodes	3,20	3.13	0.051	3,28	8.82	0.000***	6,54	51.23	0.000***	6,54	27.03	0.000***
Location × Attention	1,7	0.02	0.898	1,9	0.01	0.943	1,9	0.34	0.574	1,9	0.91	0.366
Location × Probability	1,7	0.01	0.931	1,9	0.16	0.699	1,9	0.05	0.822	1,9	0.90	0.366
Attention × Probability	1,7	3.40	0.108	1,9	3.80	0.083	1,9	0.31	0.593	1,9	7.79	0.021*
Location × Electrodes	6,42	21.92	0.000***	3,31	28.99	0.000***	3,26	1.25	0.311	3,27	11.73	0.000***
Attention × Electrodes	6,42	2.75	0.097	6,54	7.48	0.001***	3,22	3.82	0.003***	3,29	20.81	0.000***
Probability × Electrodes	3,23	1.11	0.368	4,32	0.33	0.835	6,54	1.36	0.248	6,54	12.20	0.000***
Location × Attention × Probability	1,7	0.93	0.367	1,9	1.91	0.200	1,9	0.16	0.703	1,9	0.23	0.641
Location × Attention × Electrodes	3,20	6.25	0.004***	3,29	3.95	0.016*	3,23	1.16	0.341	4,34	2.18	0.095
Location × Probability × Electrodes	4,26	0.74	0.566	3,27	0.72	0.549	3,24	0.78	0.503	3,31	0.61	0.632
Attention × Probability × Electrodes	3,19	1.84	0.178	4,32	1.61	0.202	6,54	1.35	0.253	4,34	5.72	0.002***
Location × Attention × Probability × Electrodes	3,22	0.75	0.537	6,54	1.63	0.157	3,30	1.37	0.272	3,26	0.31	0.811

^a d.f., degrees of freedom; *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.005$.

^b $n = 8$.

^c $n = 10$.

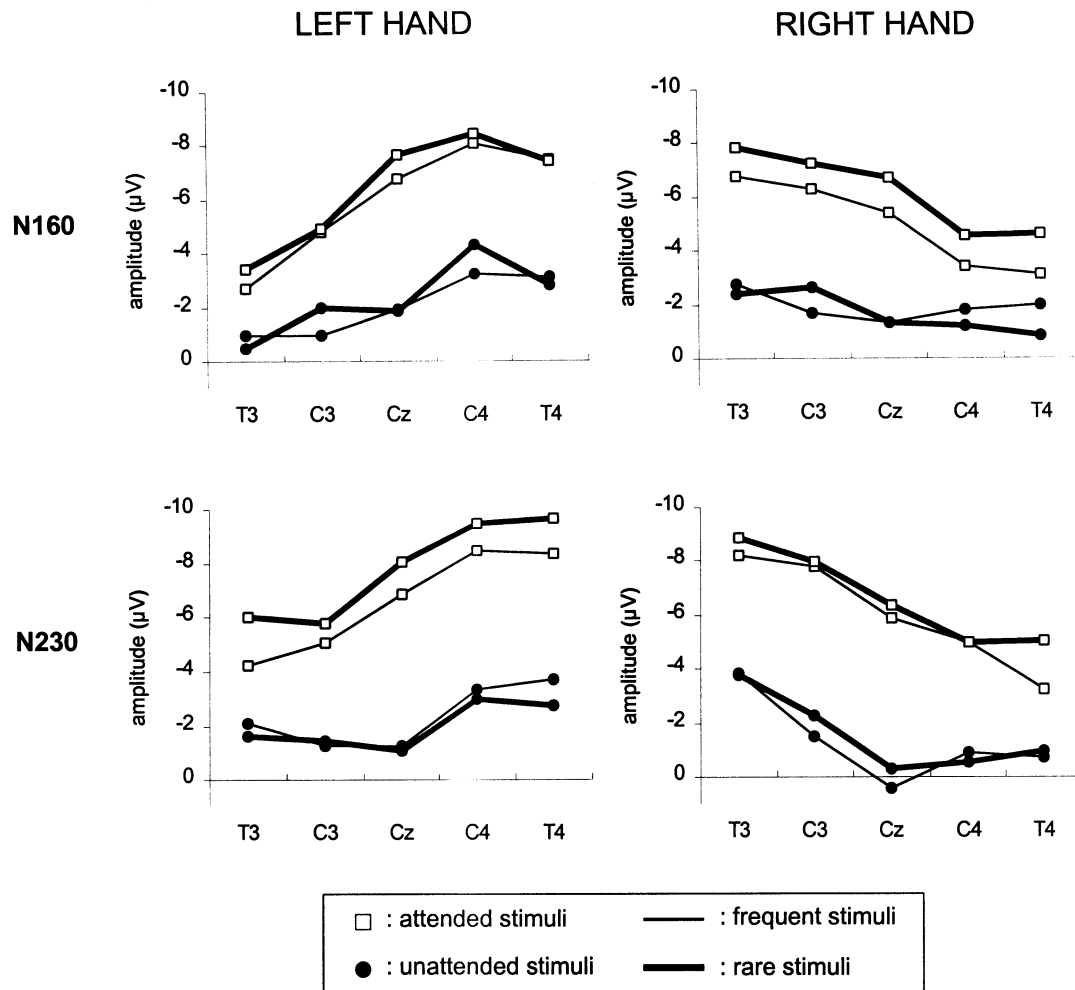


Fig. 8. Peak amplitude of N160 and N230 across the central coronal line.

Desmedt et al., 1983; Desmedt and Tomberg, 1989; García-Larrea et al., 1991), but also at 60 ms (Michie et al., 1987), and at 120–140 ms (Desmedt and Robertson, 1977; Michie et al., 1987; Desmedt and Tomberg, 1989; García-Larrea et al., 1991, 1995).

In line with the literature reviewed here, the difference in amplitude of the laser-evoked N160 and N230 between attended and unattended conditions can be attributed to spatial attention modulation of nociceptive processing. This assumption is based on the following arguments.

Firstly, stimuli from the different categories (channels) were randomized during each run, preventing subjects from knowing which hand would be stimulated at each subsequent trial. Consequently, they did not know whether the forthcoming stimulus would belong to the attended category or not. Thus, the N160 and N230 effects cannot be due to expectation or differential preparation processes (Näätänen, 1992, pp. 247–250).

Secondly, comparisons were made on stimuli belonging to the same channel (sharing the same physical features) when attention was focused on that channel and when it was focused elsewhere (e.g. Hillyard et al., 1973). The

difference in the N160 and N230 amplitudes can be attributed to change in the direction of the attentional focus, and not to change in stimulus parameters.

Thirdly, subjects were involved in the same task, providing an equivalent overall arousal state across the different conditions. As reported by our subjects, detecting rare weak stimuli among stronger ones was more difficult than detecting rare strong stimuli among weaker ones. However for each condition, LEPs obtained with the two stimulus intensities were averaged together, so that task difficulty was matched between all other experimental conditions. In each block, LEPs to attended stimuli and unattended stimuli were recorded when subjects were performing exactly the same task. Therefore, the results do not reflect a difference in task difficulty and performance. In previous studies, LEPs were recorded in different runs using different tasks. In the attention conditions, laser stimuli were often delivered alone and subjects were asked to count them or to rate the perceived intensity of stimuli. In the distraction conditions, they were presented with other kinds of stimuli involving target detection (García-Larrea et al., 1997), digit-memory or calculation tasks (Beydoun et al., 1993; Yamasaki et al.,

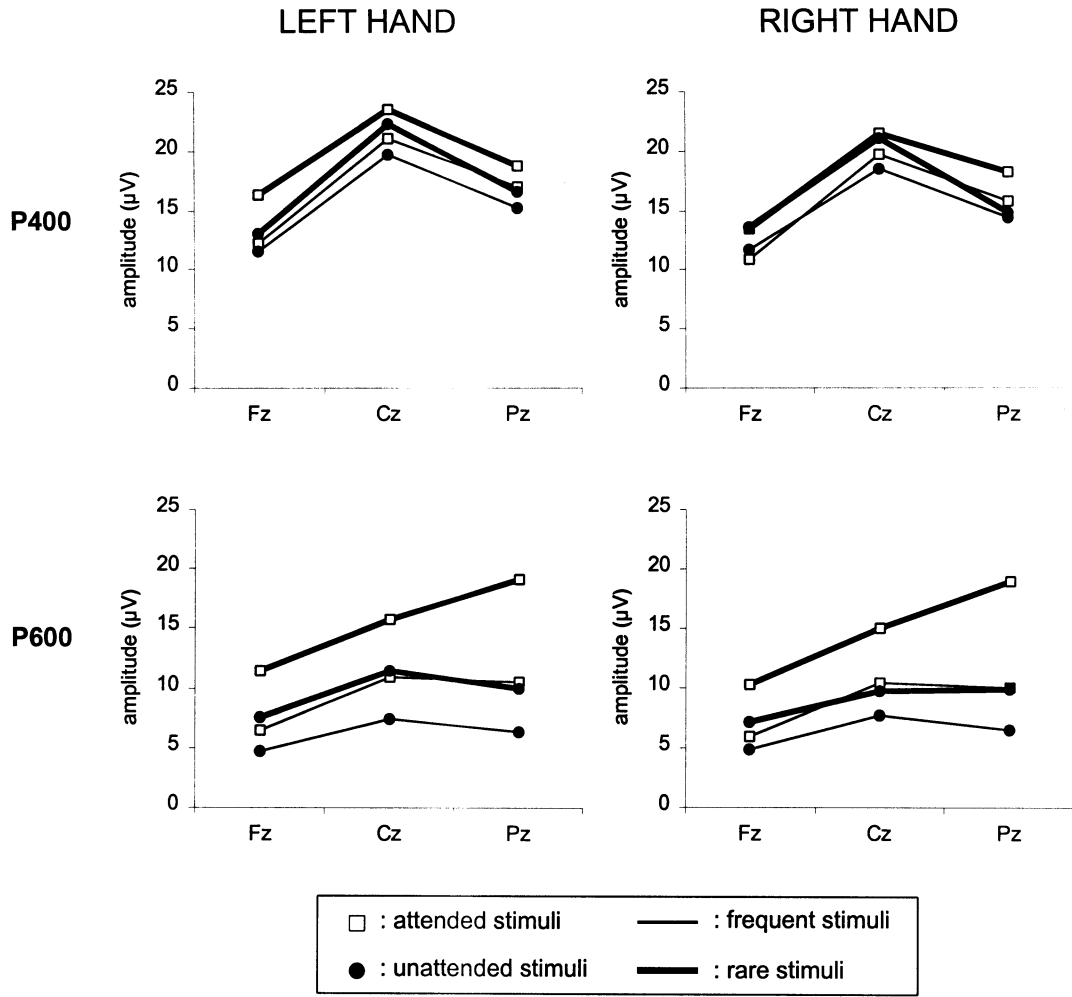


Fig. 9. Peak amplitude of P400 and P600 across the central sagittal line.

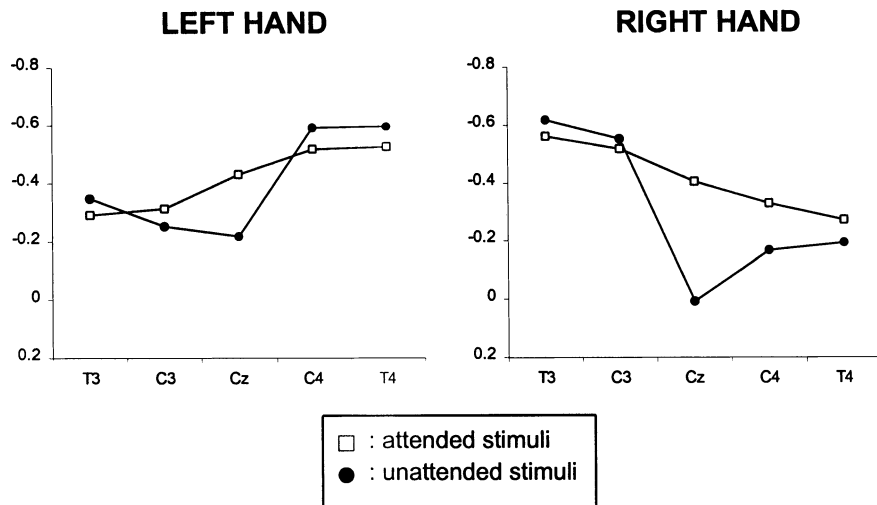


Fig. 10. Normalized peak amplitude of N230. Data to the rare and frequent conditions were integrated together for illustration.

1999), or reading task (Siedenberg and Treede, 1996). In the study of Zaslansky et al. (1996), the difficulty of the task (calculation) was not matched between the attentive and the distractive conditions.

Fourthly, N160 and N230 amplitudes for attended frequent and attended rare heat stimuli were similar. The difference between frequent and rare heat stimuli emerged only in the P400 time range. Attended frequent and rare heat stimuli were processed in the same way during the early time interval, until the intervention of processes allowing to discriminate rare from frequent stimuli. It may be concluded that during the N160–N230 time range, attended and unattended stimuli were processed differently on the basis of the direction of spatial attention only, and not on the basis of the probability and the discrimination task. Similar results were observed for the visual (Hillyard and Münte, 1984; Heinze et al., 1990; Mangun and Hillyard, 1990; Luck et al., 1993), the auditory (Schwent et al., 1976a,b; Hansen and Hillyard, 1980, 1984), and the somatosensory ERPs (Desmedt and Robertson, 1977; Michie et al., 1987; García-Larrea et al., 1991).

The larger N160 and N230 amplitudes in the attended condition strongly suggest that brain activities evoked by painful CO₂ laser stimulations between 120 and 250 ms are modulated by selective spatial attention mechanisms. In line with the sensory gain theory, it is suggested that directing attention to a specific body location modulates neural activity evoked by nociceptive stimuli in brain regions generating the N1 and N2 components. Indeed, there was no latency or waveform difference between attentional conditions. This suggests that modulation of the LEPs by spatial attention is related to amplitude enhancement of N1 and N2 rather than to the overlap with new components. Furthermore, the scalp distribution was quite similar between the attended and the unattended stimuli, at least on lateral electrodes³. Topography was strongly location-dependent: both N160 and N230 disclosed scalp distribution contralateral to the stimulated hand.

While a contralateral topography of N160 is in good agreement with previous studies, the contralateral distribution of N230 contrasts with the central symmetric distribution usually found in previous reports (Treede et al., 1988; Kunde and Treede, 1993; Miyazaki et al., 1994; Spiegel et al., 1996; Valeriani et al., 1996). It is worth noting that the asymmetry of the N230 distribution is not incompatible with the hypothesized brain generators of N2. Indeed, Tarkka and

Treede (1993) proposed that N2 could be explained by two dipoles located in the contra- and ipsilateral superior banks of the sylvian fissure (SII). These two dipoles were also found in other studies, but did not coincide very well with N2 (Bromm and Chen, 1995; Valeriani et al., 1996). Bilateral SII responses were confirmed by subdural (Lenz et al., 1998a) and intracortical (Frot et al., 1999) recordings. Bilateral insular areas (Frot et al., 1999) and medial temporal areas (Watanabe et al., 1998; Valeriani et al., 1996) were also proposed to be involved in the laser-evoked N2. These data suggest that N2 originates from bilateral activations, which can result in a central scalp distribution. Consequently, as it is conceived that gain control mechanisms are involved in attentional modulation of LEP negativities, we may assume that, in the present study, spatial attention operated by increasing the activity of the contralateral areas generating N1 and N2. As a consequence, a greater response was recorded in contralateral areas relative to ipsilateral ones, which led to a shift of N2 distribution toward the contralateral side.

However, this hypothesis is not sufficient as contralateral topography was also found for N230 elicited by unattended stimuli. It could be suggested that, relative to previous LEP studies, attentional mechanisms were also involved in mid-latency LEPs triggered by unattended stimuli. Maybe each laser stimulus presented at a location induced automatic displacement of the attentional focus to this location (e.g., Jonides, 1981), leading to a facilitation of the processing in the contralateral brain areas of the next stimulus presented at the same location. This processing should be further facilitated when the location was additionally attended. However, in the present task, stimuli had the same likelihood to be preceded by a stimulus at the same and at the other location. The present data did not allow to confirm these assumptions which will need further empirical evidence.

Finally, although a lateral presentation of stimuli was

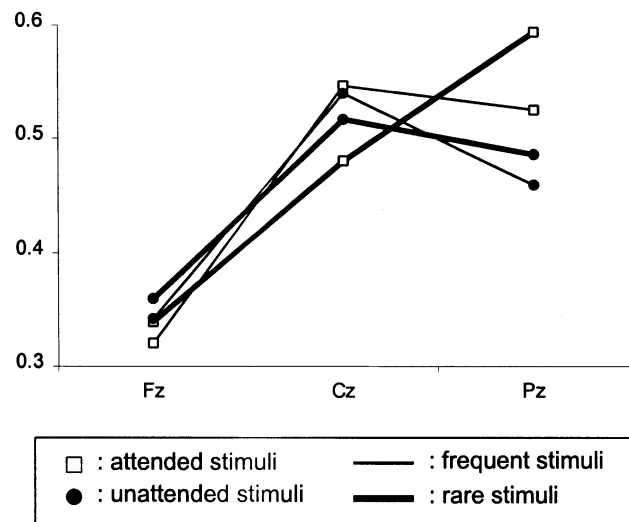


Fig. 11. Normalized peak amplitude of P600. Data to the right-hand and left-hand conditions were integrated together for illustration.

³ When the comparison of the scalp distributions included Cz, the N230 amplitude in the unattended condition appeared depressed at Cz relative to the lateral leads (Fig. 10). Assuming that the N230 offset and the P400 onset are partially overlapped at Cz, one may speculate that the small-amplitude N230 in the unattended condition was masked by P400 at Cz. A positive-going activity could be seen at the end of the negative components in the maps of Fig. 6. An alternative explanation would be the presence of new LEP components with central distribution, triggered either by attended stimuli with negative amplitude or by unattended stimuli with positive amplitude such as the rejection positivity suggested by Alho et al. (1987b).

Table 2
ANOVA for LEP latencies^a

Factors and interactions	N160 ^b			N230 ^c			P400 ^c			P600 ^c		
	d.f.	F	P	d.f.	F	P	d.f.	F	P	d.f.	F	P
Location	1,7	0.00	0.951	1,9	0.00	0.966	1,9	0.55	478	1,9	0.07	0.797
Attention	1,7	9.68	0.097	1,9	0.01	0.931	1,9	0.16	0.699	1,9	4.33	0.067
Probability	1,7	2.27	0.176	1,9	6.94	0.027*	1,9	0.85	0.381	1,9	0.11	0.753
Electrodes	3,20	1.63	0.215	6,54	3.39	0.039*	6,54	6.35	0.000***	3,31	2.70	0.056
Location × Attention	1,7	0.00	0.983	1,9	1.40	0.266	1,9	0.68	0.432	1,9	0.00	0.950
Location × Probability	1,7	0.67	0.439	1,9	0.28	0.609	1,9	0.34	0.575	1,9	0.10	0.756
Attention × Probability	1,7	1.70	0.234	1,9	0.09	0.776	1,9	0.77	0.402	1,9	0.02	0.894
Location × Electrodes	6,42	1.20	0.327	6,54	2.12	0.109	3,27	1.94	0.148	4,33	0.46	0.764
Attention × Electrodes	2,15	0.31	0.751	3,31	0.19	0.925	3,25	2.72	0.070	4,36	1.26	0.303
Probability × Electrodes	3,23	0.61	0.632	3,30	2.38	0.084	6,54	1.60	0.165	3,26	0.19	0.898
Location × Attention × Probability	1,7	2.76	0.140	1,9	0.88	0.373	1,9	1.62	0.235	1,9	0.47	0.509
Location × Attention × Electrodes	2,15	0.36	0.724	4,32	0.79	0.528	3,30	0.51	0.693	6,54	0.32	0.922
Location × Probability × Electrodes	3,23	1.13	0.360	6,54	0.30	0.935	4,32	2.72	0.052	3,29	0.18	0.919
Attention × Probability × Electrodes	3,20	0.98	0.421	3,27	0.99	0.411	3,29	9.03	0.043*	3,27	1.35	0.279
Location × Attention × Probability × Electrodes	3,21	1.07	0.382	3,28	0.91	0.453	3,23	0.78	0.500	4,35	0.68	0.609

^a d.f., degrees of freedom; *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.005$.

^b $n = 8$.

^c $n = 10$.

used in previous studies, no distribution asymmetry of N230 was observed. Two reasons may be put forward. Firstly, in the present study, stimuli were administered to different body regions at random, while the other studies recorded LEPs from stimulation of one body region at a time, without any concurrent stimuli at another location. Thus, in those studies, displacements of the attentional focus were not required. Second, ISI was much shorter in the present study than in the previous ones (Beydoun et al., 1993; Zaslansky et al., 1996; García-Larrea et al., 1997; Yamasaki et al., 1999). Many studies proposed that short ISI is an important factor to observe selective attention effect (Schwent et al., 1976a; Desmedt and Robertson, 1977; Woldorff and Hillyard, 1991). The onset of the auditory attentional effect is shorter with shorter ISI (Hansen and Hillyard, 1984; Teder et al., 1993). It can be assumed that in previous studies the ISI was too long to recruit spatial attentional mechanisms as early as the N160–N230 latency. Other factors could have favored selection effects at early LEP latencies: random stimulation of both hands providing large separation between attended and unattended channels (Hansen and Hillyard, 1980; Alho et al., 1987a,b; Mangun and Hillyard, 1988; Teder-Sälejärvi and Hillyard, 1998) and difficulty of the task (discrimination of energy levels) requiring the subjects to allocate more resources to the attended stimuli (Schwent et al., 1976b; Eimer, 1993; Handy and Mangun, 2000).

4.2. The positivities P400 and P600

The P400 and P600 components showed different amplitude modulations and topographies across experimental conditions. The maximum peak amplitude of P400 was

recorded at Cz in all conditions. The P600 was evoked by the attended rare stimuli with a parietal topography. In the other conditions, LEP activity at this latency appeared rather as a small shoulder in the P400 slope when returning to baseline. A P600 component, clearly distinct from P2, has already been observed in oddball designs in which rare and frequent stimuli were delivered on different parts of the same hand (Towell and Boyd, 1993; Kanda et al., 1996; Plaghki, 1997). Siedenberg and Treede (1996) found similar parietal positivity (P570) by subtracting LEPs to non-targets from LEPs to targets. In all these studies, including the present one, rare laser stimuli to be detected by counting or key-pressing, elicited a parietal positivity peaking later than P2 at around 550–600 ms. These data provide evidence that the laser-evoked P600 (or P570) corresponds to P3b generally observed in oddball paradigms. Indeed, P3b is observed (1) for the rare stimuli, (2) with parietal topography, (3) when subjects are engaged in the active detection of the rare events (Squires et al., 1975). Additionally, we showed a clear parietal P600 evoked by attended rare target stimuli, but not by rare stimuli delivered outside the focus of attention.

Zaslansky et al. (1996) proposed that the laser-evoked P2 itself could reflect P3b-like activity. They delivered frequent and rare stimuli and, in counterbalanced sessions, the subjects were instructed to count either the rare or the frequent stimuli. The authors found larger P2 for rare stimuli irrespective of the instructions. Despite their conclusion, there is evidence that their P2 did not reflect only a P3b component. Firstly, as reviewed above, there is evidence that P3b elicited by laser stimuli has a later latency. Secondly, Zaslansky et al. (1996) observed similar P2 amplitudes for rare and frequent targets, while the larger

amplitude was seen for the rare non-targets that had not to be detected. Thirdly, the amplitude of their positivity was equivalent at Cz and Pz. In the other studies and the present one, P2 was larger at Cz and P600 to rare targets was larger at Pz. Fourthly, they did not take into account the latencies for analysis. Some of their subjects displayed a broad and biphasic positivity. In some of them, the difference between rare targets and frequent non-targets was more clear in the second phase. Consequently, their LEPs recorded in oddball tasks could probably contain a P3b that was partially overlapped with P2, but it was not identified by direct inspection of original LEP traces as in the study of Siedenberg and Treede (1996). From the present data, it can be concluded that P2 is not a P3b-like component, because such a component should have been seen for rare targets at a longer latency with parietal topography.

Given the latency and topography data, P400 observed in the present study was probably the P2 classically observed in LEP studies. However, we observed that P400 was modified by the probability of the stimulus, as in the study of Plaghki (1997). Furthermore, unlike P600, we found that this probability effect was independent of attention. Indeed, a larger P400 amplitude to attended rare compared to attended frequent stimuli was found, as well as to unattended rare compared to unattended frequent stimuli. Such P400 modulations are similar to those observed for P3a. P3a is suggested to be associated with the orienting response (Halgren and Marinkovic, 1995) and to reflect involuntary switch of attention to unexpected deviant events interfering with the ongoing processing (Knight, 1996; Escera et al., 2000). P3a is elicited by rare stimuli, with frontal-central topography and earlier latency than P3b, and unlike P3b, even when subjects do not pay attention to the stimuli (Squires et al., 1975) or when deviants are task-irrelevant (Escera et al., 1998; Katayama and Polich, 1998). P3a could also be evoked by task-irrelevant novel stimuli in the visual, auditory, and somatosensory modalities (Courchesne et al., 1975; Yamaguchi and Knight, 1991; Knight, 1996).

It could be that the present P400 modulation by stimulus probability reflects similar mechanisms. The main evidence is the larger P400 amplitude for rare stimuli, whether attended or not, strongly suggesting that the modulation of LEPs in the P400 time range is less attention-dependent than the subsequent P600. Bruyant et al. (1993) found P3a for somatosensory rare stimuli when the frequent stimuli were targets. In the same way, the laser-evoked positivity of Zaslansky et al. (1996) was larger for rare non-targets than for frequent targets and non-targets. Our P400 was centrally oriented, whereas the P3a distribution was rather fronto-central. However, some studies have pointed out that the somatosensory P3a is more posterior than the auditory and visual ones (Yamaguchi and Knight, 1991; Bruyant et al., 1993).

The relative independence of P400 from attention in the present study is in disagreement with previous LEP studies showing a reduction of the amplitude of P2 when attention

was directed to another task (Beydoun et al., 1993; Zaslansky et al., 1996; García-Larrea et al., 1997; Yamasaki et al., 1999). However, P3a is not entirely attention-independent (Loveless, 1986; Schröger, 1997; Harmony et al., 2000). P3a was generally not observed for unattended rare stimuli in the auditory selective attention studies (see Näätänen, 1992). It was only observed when unattended rare stimuli were novel (Woods, 1992). Furthermore, P3a was increased for similar novel stimuli on the attended channel. Unlike studies on selective attention in other modalities using focused attention paradigms, we observed P3a-like probability effect in the unattended channel, maybe because nociceptive stimuli are more obtrusive in nature and more attention-catching than in other sensory modalities (see Näätänen et al., 1982; Loveless, 1986), even when they are presented as deviant among other types of nociceptive stimuli. Thus, unattended rare nociceptive stimuli presented on one body location could induce an attentional switch from the actual focus of attention to another body part, even when the subjects are engaged in selective operations in order to preferentially process inputs from the latter body location and to avoid interference from the former one.

From the present data, it cannot be established whether the laser-evoked P2 itself shares common processes with the P3a, or if the actual P400 modulation by the probability of the stimulus was due to elicitation of a P3a at the same time range as P2. The similarity of topography and the minor change in latency across conditions seem to plead for a modulation of the same component, however, overlap cannot be ruled out.

4.3. Conclusions

It was shown that different stages of the nociceptive processing in the brain could be modulated by specific aspects of the present task and related attentional processes. Two main findings were obtained. Firstly, the amplitude of the LEPs was modulated by the direction of spatial attention to one body location when different body parts were stimulated at random. This attentional modulation occurred as early as 120 ms, which is earlier than in previous studies. Secondly, attended rare targets elicited parietal P600 that possesses the main characteristics of P3b. Finally, the intermediate laser-induced responses (P400) were modified by probability of the stimulus, whether attended or not. However, these modifications need further investigations for more precise explanation.

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