

Original article

## Contribution of attentional and cognitive factors to laser evoked brain potentials

### Modulation attentionnelle et cognitive des réponses évoquées par laser

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#### Abstract

Painful stimuli delivered by infrared laser stimulators elicit laser-evoked potentials (LEP) or magnetic fields in respective electroencephalogram (EEG) and magnetoencephalogram (MEG). Evidence is reviewed that LEP represent a series of event-related potentials (ERP) that depend on vigilance and arousal, selective spatial attention and contextual task variables. Paradigms adopted from other stimulus modalities in the assessment of attention and cognition in ERP and applied to LEP allow the view that middle-latency (N1) and long latency (N2–P2) components of LEP can be overlapped or supplemented by endogenous components such as the processing negativity and distinct members (P3a and P3b) of the “P300” activities, each of which is considered in detail in this review. This composite entity needs to be considered when LEP are experimentally or clinically used in the assessment of sensory and cognitive phenomena and abnormalities of pain sensation.

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#### Résumé

Les stimulations cutanées nociceptives par laser infrarouge évoquent des potentiels évoqués (PEL) ou des champs magnétiques respectivement dans l'électro-encéphalogramme (EEG) et le magnéto-encéphalogramme (MEG). Nous discutons ici l'évidence que les PEL peuvent être interprétés en tant que « potentiels liés à l'événement », dépendants de la vigilance, de l'attention spatiale sélective et du contexte expérimental. L'application aux PEL de protocoles habituellement utilisés pour l'étude de ces variables cognitives a permis de mettre en évidence que toutes les composantes des PEL (N1, N2 et P2) peuvent être modulées par l'attention et par la vigilance, avec également superposition de composantes endogènes telles la négativité de traitement (*processing negativity*), et différents membres de la famille des réponses « P3 » (P3a et P3b). Chacune de ces modifications est discutée en détail dans cette revue. Cet ensemble de modulations–superpositions doit être considéré lorsque les PEL sont utilisés expérimentalement ou en clinique pour l'évaluation de la perception douloureuse ou de ses anomalies.

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**Mots clés :** Potentiels évoqués laser ; Vigilance ; Attention ; Potentiels cognitifs ; N1 ; P3

#### 1. Introduction

Evoked potentials and their magnetic counterparts, evoked fields (EFs), are transient deflections of respective electroencephalogram (EEG) and magnetoencephalogram (MEG) that systematically follow sensory events at or around

characteristic time points. They result from a sudden increase of synchronized postsynaptic activity in large numbers of quasi-parallel neurons generating a summated extracellular field. Part of the magnetic component is directly measurable by MEG sensors located outside the head, whereas the electric component is volume-conducted to the surface of the head and becomes measurable through EEG scalp electrodes. Several stimulus repetitions and averaging of peristimulus activity are usually necessary to extract evoked

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responses from the ongoing EEG/MEG and allow their reliable parameterization according to amplitude and latency measures.

Evoked neuronal activity in circumscribed subcortical and cortical areas that represent early information processing stages typically requires artificial and simple stimulus types, such as broadband clicks or sinusoidal bursts in auditory-evoked potentials (AEP), checkerboard pattern reversal in visual-evoked potentials (VEP), or electrical nerve trunk stimulus in somatosensory-evoked potentials (SEP). These stimuli possess sufficiently steep stimulus rise times and the elicited EPs are called *sensory* or *exogenous components* because they are highly sensitive to physical stimulus attributes such as modality, intensity, duration, or repetition rate. In contrast, complex tasks involving psychological stimulus attributes such as novelty, relevance or memory recall, not only modify a subset of exogenous responses, but also generate *endogenous components* reflecting the engagement of higher-order functional specificities of perception, cognition, attention and behavioral responses. The term ‘event-related potentials’ (ERP) is meanwhile widely used to include both exogenous and endogenous components.

Pain is a complex sensory, cognitive and affective phenomenon, and therefore, intrinsically involves both physical and psychological stimulus attributes. Mor and Carmon [46] first introduced the methodology of laser-evoked potentials (LEP) into the assessment of pain in humans. Several authors demonstrated the use of the LEP method to document nociceptive abnormalities in neurological and pain patients ([6,9,20,25,37–39,64,65], see also [66], this volume). However, LEP appear in the time range where exogenous and endogenous components occur. Since standard LEP protocols designed for the objective documentation of nociceptive deficits (or analgesic effects) involve randomization of stimulus intensities and the assignment of particular tasks to the subjects such as focusing to the stimulus site and rating the perceived intensity [5,56,58], some interaction of sensory and cognitive variables is most likely. Although in most clinical studies the design explicitly accounted for the importance of arousal, habituation and selective attention upon the amplitude of LEP in keeping these factors constant across the target variables (e.g. normal versus affected dermatome), several authors addressed the precise validity of the various LEP components in terms of their differential sensitivity towards the physical and psychological manipulations of the laser stimulus, with results not always concordant [23,34–36,49,57,62,70–72].

The diversity of experimental paradigms that were used to examine attentional effects on LEP reflects the different aspects of attentional phenomena. Thus, before going into the details of the various studies, the next section will briefly review current concepts and neurophysiological substrates of attention. Converging information on this issue is provided by studies that aimed to identify the brain areas that generate the various LEP components by the dipole reconstruction technique of multi-lead data (see [24], this volume).

## 2. Components of attention

Attention is not a single neurophysiological entity. Among many authors, Parasuraman et al. [53] describe different major components of attention that rely on a finite set of brain processes being hierarchically organized and interacting with each other. A basic component serves the maintenance of behavioral goals over time and is largely synonym to *arousal*, *vigilance*, *alertness* or *sustained attention*. It also involves the regulation of the sleep–wakefulness cycle. Cholinergic and noradrenergic ascending systems originating in the reticular formation and the locus coeruleus and dopaminergic projections in the striatum are regarded important for this function referred to as “the vigilance network” by Posner and Petersen [52]. Another component concerns the bias or filtering of task-relevant against irrelevant information. It serves to cope with capacity limits of central information processing which cannot deal with the huge amount of input from a large variety of sensors in different modalities at the same time. This component is often referred to as *selective* or *focused attention* and, according to Posner and Petersen [52], depends on the posterior attention network that includes brain structures such as the superior colliculus, thalamic pulvinar and the posterior parietal cortex.

Selective attention is often metaphorically described by a ‘spotlight’ or ‘cocktail party’ effect, which emphasizes the phenomenon that the focus of awareness can momentarily fluctuate between sensory objects, features or locations sometimes without overt orientation in the form of eye or head movements. It is believed that the gating of the afferent flow of information within attentional channels (i.e. the set of stimuli benefiting from selective attention) optimizes functional efficiency even at very early stages of modality-specific cortical processes [14,15,17,19]. Closely linked to this function is a supervisory component of attention that temporarily intervenes into ongoing performance when called for by new relevant, unfamiliar or potentially dangerous information, the detection of performance errors, or when internal representations need to be continuously updated, i.e. during working memory operations. This component is often referred to as *executive attention*, largely governed by the anterior attention network *sensu* Posner and Petersen [52] that comprises the anterior cingulate, medial and lateral prefrontal cortex areas and the supplementary motor area.

## 3. Event-related potential correlates of attention

Studies that looked for the effect of selective attention upon ERP typically involved a series of target and non-target stimuli presented to an attended sensory channel (e.g. one ear) while the same series of stimuli were to be ignored in another sensory channel (e.g. the other ear). Computation of difference waves from ERP following stimuli presented to the ignored channel subtracted from ERP following the same

stimuli presented to the same sensory channel when it was attended consistently yielded negative components in latency ranges between 50 and 150 ms. These components were first described for auditory stimuli and referred to as negativity difference wave (Nd) [28] or processing negativity [47,48], and similar negative enhancements were also observed for visual [26] and somatosensory stimuli [13,22,44].

It remained for a longtime ambiguous and controversial whether the attentional effect in the 50–150 ms range relies on simple facilitation of primarily exogenous (sensory) processes, which appear in the same latency range, or to the existence of overlapping, purely endogenous potentials. Different studies using whole-scalp topographic data strongly supported that (a) activity in this latency range reflects activation of several overlapping neural populations, and (b) both modulation of exogenous potentials and superimposition of genuinely endogenous responses, not discernible in the absence of attention and generally known as ‘processing negativities’, are likely to coexist in attentional contexts (e.g. [22,30,43]). The observation that changes in the ‘N1’ component (50–150 ms) obviously occur before perceptual identification and cognitive decision in response to the eliciting stimulus, differentiates these ERP phenomena from those appearing later after stimulus onset, such as the P300 or P3 wave, that crucially depend on such processes.

Sutton et al. [61] first described that task relevance and occurrence probability of auditory stimuli represent key phenomena of P3 elicitation in the human EEG, which Desmedt et al. [12] confirmed almost simultaneously for somatosensory stimuli. Although P3 is generally largest for task-relevant and rare stimuli, deviant or highly intrusive stimuli from outside the focus of attention can also evoke a smaller variant of P3, with shorter latency and more frontal topography than the one commonly found in response to designated targets. This “novelty-P3” [11] or “P3a” [59] was considered to index an orienting reaction to intrusive changes in the environment, and thus differentiated from the original P3, hitherto designated as “P3b”. These observations also demonstrated that the P3 wave is not a unitary phenomenon, but rather a family of waves differing in their brain generators and in their psychological correlates. It is currently accepted that the family of P3 waves represent late stages in information process, related to processes such as memory encoding/updating, access of information to consciousness, and closure of a perceptual epoch (reviews in [27,51]).

Thus, it became obvious that when belonging to an attended channel, sensory stimuli may experience facilitated processing causing negative amplitude shifts or “processing negativities” in middle and long-latency ERPs. Furthermore, processes such as orienting to, and detection of, sensory targets, memory encoding and recall, decision making and context closure are likely to induce the presence of P3-like events reflecting later stages of information processing, and therefore, developing at longer latencies.

#### 4. LEPs and vigilance

Long duration mental tasks yield a characteristic vigilance decrement that can be measured subjectively or by behavioral indicators such as reaction time [53]. Similarly, amplitudes of pain relevant evoked potentials after electrical stimuli [2,7,16,45], painful chemical stimulation of the nasal mucosa [32] and laser stimulation [1,5,8,68] are strongly attenuated by habituation and decreases of vigilance over time. Although pain generally enhances arousal, the LEP test situation is characterized by repeated laser stimuli, presented at long inter-stimulus intervals in quite monotonous long stimulus blocks, which contribute to the vigilance decrement in LEP amplitudes. Beydoun et al. [3] examined subjects who they allowed to fall asleep after 1 day of sleep deprivation to look for LEP during different sleep stages compared to normal wakefulness. They demonstrated the abolition of the N2–P2 component at the vertex position during sleep stage II, defined by the appearance of sleep spindles, and its strong amplitude attenuation during sleep stage I, defined by drop-out of alpha activity and appearance of lateral eye movements.

Furthermore, decreases of LEP amplitudes also accompany sedation and drowsiness when induced pharmacologically using benzodiazepines [72] or subanaesthetic isoflurane [55]. Because laser pain ratings also diminish with decreases of pre-stimulus alertness, *it is difficult to differentiate drowsiness or sedation from analgesia by the LEP alone*. Evaluation of alpha activity [3,56] or the control of ERP following stimuli of non-nociceptive modalities, e.g. tones, either interspersed within the laser series or presented within separate tasks of similar block lengths as the laser paradigm [40,41] can offer viable solutions. Lorenz et al. [41] differentiated vigilance from analgesic effects in laser EPs by combining LEP recording with AEP, including cognitive P3. They found laser-induced pain ratings and the LEP P2 component attenuated by about 35% after initiation of an oral treatment with morphine in patients suffering from chronic non-malignant pain. However, late AEP following tones that prompted the patient to verbally rate the painfulness of each laser stimulus, as well as AEPs and P3 from an auditory oddball task yielded unchanged or even slightly enlarged amplitudes. Because mood ratings and reaction times also indicated improvement of the cognitive status, probably due to the release from pain as workload stressor, the obvious absence of sedation in this study allowed the LEP attenuation to be identified as analgesic effect.

#### 5. The LEP ‘vertex complex’ (N2–P2) and attention

The first systematic studies on attentional effects on LEP concentrated on the vertex N2–P2 potential and compared attended versus distracted stimulus conditions [3,18,23,57,70,71] or used oddball paradigms to look for P3-like potentials in LEPs [29,34,35,57,62,71]. The vast ma-

jority of these studies reported strong enhancement of the vertex complex N2–P2 with increased attention [3,18,23,57,70,71]. Some studies, however, found attention-related enhancements for N2, but not P2 [34], and others reported no change in either N2 or P2 when comparing target versus non-target stimuli [29,62]. These discrepancies may be accounted for, at least in part, by the respective experimental paradigms. Experiments where attentional enhancement of vertex (N2–P2) responses was observed compared LEPs during attention directed *either* to the laser stimuli *or* distracted toward other stimulus modalities, memory tasks or introspection [3,18,23,57,70,71]. Thus, all these experiments compared *inter-modal* attentional effects (i.e. effects linked to a shift of attention across different sensory modalities or tasks). In contrast, the N2–P2 did not change amplitude when comparisons concerned target versus non-target stimuli, either delivered to the same hand [34,62] or even to different hands [29], indicating that a substantial part of the enhancing effect on LEP vertex potentials was linked to focusing on a particular stimulus modality—in this case laser pulses. More recent data from Legrain et al. indicate that, in addition to this inter-modal attentional effect, the N2 component of LEPs is also sensitive to the *spatial direction* of attention within a same sensory modality. Thus, in a series of elegant experiments, these authors showed that the LEP N2 was increased in response to laser stimuli at selectively attended body locations, whether they were target or non-targets, relative to identical laser stimuli delivered to regions outside the attentional focus [34,35].

The vertex LEP response appears, therefore, to be modulated by at least three sources of attentional changes. Besides a non-specific effect of vigilance and arousal (see previous section), it can be described as an *inter-modal* attention effect, making N2 and P2 LEPs decrease whenever attention is drawn towards other sensory modalities or tasks, and an *intra-modal*, spatial attention effect, whereby the N2 increases as a function of the spatial orienting of attention. Interestingly, such three sources of variance have been also described in the vertex response within other sensory modalities (e.g. [48,50]).

## 6. LEPs and the P3 (P300) response

In spatial discrimination tasks in which a series of laser stimuli were applied at two locations according to the classical oddball factors—occurrence probability (frequent versus rare) and task relevance (target versus non-target)—most authors described a separate, more posteriorly distributed “laser P3”, which followed P2 in response to rare targets and was considered as functionally equivalent to the cognitive “P300” wave [29,34,35,57,62]. In most studies P2 and P3 laser responses could be separated on the basis of latency and topographical dissimilarities [29,34,35,57,62]. Only Zaslansky et al. [71], who also found rare targets to elicit a greater LEP positivity than frequent or ignored laser stimuli, sug-

gested that the laser P2 was in fact to be considered as functionally equivalent to the cognitive P3 (or P300) wave, indicating the implicit cognitive appraisal of painful stimuli. However, this hypothesis does not match current knowledge on the latency and topographic features of these two responses. For instance, given the occurrence of a P2 at 250 and a P3 at 400 ms after electrical finger stimuli [13], which predominantly depend upon rapidly conducting A $\beta$ -fibers, one should expect a P3 after activating slowly conducting A $\delta$ -fibers by laser stimuli not before 500 ms, which has been indeed the consistent result in studies that described separate P2 and P3 waves in laser oddball paradigms [29,34,35,57,62]. Another source of evidence that the standard laser P2 and P3 represent different neurophysiological phenomena is provided by studies in patients. Yamamoto et al. [69] compared auditory oddball-P3 and LEPs in demented patients. The degree of cognitive decline, assessed by psychological tests, correlated significantly stronger with auditory P3 latency than with P2 latency of LEP. Twelve of the 25 patients had absent auditory P3, but only the four most severely demented patients also had absent LEP. Furthermore, auditory P3, but not LEP correlated with age in these patients. Thus, the authors concluded that pain perception may be impaired by dementia, but this aspect of cognitive decline is different from the alterations indicated by the oddball P3. Lorenz et al. [42] examined a patient with sensory loss in one arm due to a conversion disorder. This patient exhibited normal early (N20–P30) and late (N150–P250) electrical median nerve SEP and normal LEP after stimuli presented to his affected arm, which the patient reported not to feel at all. However, when using an oddball paradigm with rare and frequent electrical stimuli at respective affected and normal arms, no P3 could be elicited to target stimuli in the affected (insensitive) hand, while a normal P3 to targets appeared after stimulation of the healthy side. This finding suggested that P3, unlike LEPs, involves an active goal-directed use of sensory information based on a given task context, a function that may have been selectively impaired for sensations in the affected body region in this particular condition of conversion disorder.

Although most studies yielded a quite convincing view that the laser P2 is different from the classical P3b component, it remains open whether it may be equivalent to a P3a component. As already mentioned above, P3a appears more frontally distributed and is linked to an involuntary shift of attention towards novel and salient stimuli outside the attentional focus. Corbetta and Shulman [10] recently reviewed the evidence from human functional brain imaging that partially segregated networks of brain areas—a dorsal versus a ventral fronto-parietal system—carry out goal-directed (top-down) versus stimulus-driven (bottom-up) attentional functions, respectively. Two recently published papers by Legrain et al. [34–36] in the working group of Leon Plaghki addressed the distinction of P2, P3a and P3b by carefully designed and comprehensive experiments. The authors systematically varied no-task, rare target, and rare distractor



properties of painful laser stimuli and found that (a) distinct P3a (centro-frontal) and P3b (centro-parietal) can be elicited in LEPs to actively attended or deviant stimuli, and (b) at least an early part of the LEP P2 positivity is independent of these two P3 activities. However, it also appeared from these experiments that the LEP P2 amplitude was increased by rare and strong nociceptive stimuli delivered out of the focus of attention. This was labeled the “laser P400 effect”, which enhanced the P2 amplitude without much latency change, and was considered as a genuine equivalent of a P3a, thus reflecting the automatic engagement of an orienting reaction toward suddenly arriving painful events [36]. It appears, therefore, likely that under certain circumstances *P3a-like activities may overlap the late portions of LEP P2*, in a similar way as a partial overlapping of these two responses has been suggested to occur in auditory EPs [21].

## 7. The LEP N1 wave and attention

With the more recent use of multi-channel EEG and MEG, several groups consistently recognized the existence of a middle-latency negative component (N1) over temporo-parietal cortex areas in LEP [4,33,63,67], which prompted the study of its dependence upon attention. Garcia-Larrea et al. [23] compared LEPs during attentive and distractive conditions by having subjects either count each laser stimulus (and report the number at the end of the block) or disregard the laser stimuli and count occasional interruptions of white noise delivered through earphones. Whereas the vertex N2–P2 amplitude diminished during distractive compared to attentive conditions in a significantly correlated manner with subjective pain ratings, the N1 wave at mid-temporal electrode positions remained largely unaffected. Yamasaki et al. [70], who recorded electric and magnetic responses to laser stimuli in neutral or distractive conditions (active distraction consisting of mental arithmetics and a memory task) reported similar results. Both vertex N2–P2 in EEG and the corresponding late LEFs were significantly attenuated during the two distractive conditions, while the early magnetic M1 (corresponding to LEP N1) remained unaltered in both amplitude and dipole strength. In contrast, Nakamura et al. [49] found a significant effect on the magnetic M1 when comparing different levels of attention, namely a no task condition, a standard intensity rating task and a highly spatially focused task. In the latter, subjects had to evaluate the validity of auditory cues presented before each laser stimulus, which either correctly or incorrectly announced the applied laser intensity. They found the amplitude and dipole strength of the magnetic counterpart of the N1 wave, localized within the contralateral secondary somatosensory cortex, enhanced during standard rating versus no-task conditions, but saw no further effect during enhanced attentional focusing.

The discrepancies between these three reports are not easy to explain. Interestingly in both Garcia-Larrea et al. [23] and Yamasaki et al. [70], a small attention-related increase of

contralateral N1 was apparent in grand averages (see their respective Fig. 1), although it did not reach significance. Less sensitivity of statistical analyses due to lower signal–noise ratios than that obtained by Nakamura et al. [49] may thus explain the different results. However, an alternative explanation of the divergences may derive from changes in the arousal level. Although all three studies tried to guarantee a stable level of vigilance and arousal across conditions, such stability may have been better ensured in studies that used active and demanding distractive tasks as a control [23,70]. Under this assumption, part of the N1 effect found by Nakamura et al. may have been related to a change in the overall vigilance between the ‘no task’ and the ‘task’ situations. The fact that in Nakamura et al.’s study, the N1 did not increase further during a second task condition, despite increased attentional demands, also supports the hypothesis that a substantial part of their ‘N1’ effect may have been linked to a general arousal increase between conditions 1 and 2, with a ceiling effect afterwards.

Legrain et al. [34] adopted a more elegant approach, which allowed testing both the oddball factor (rare target versus frequent non-target) and the selectivity of spatial attention (attend versus ignore) independent from each other within the same paradigm, and ensuring stability of the overall vigilance level. These authors delivered laser stimuli of two different intensities to both hands. For each hand, one intensity was rare and the other frequent. Subjects had to count rare stimuli on one hand and ignore all stimuli delivered to the other hand. They found that frequent and rare laser stimuli presented to the attended hand elicited greater amplitudes of all negative waves, including N1 (N160) and N2 (N230), components than identical stimuli to the same hand when it was ignored, and suggested the existence of a processing negativity in the LEP in analogy to similar experiments in other sensory modalities (see above). The oddball factors (rare versus frequent) did not affect N1 and N2 waves. Notably, only the negative deflection of the N1 wave over temporal leads was enhanced by attention, whereas its positive midline counterpart (P1), which is believed to arise from the same dipolar generator as N1 ([67], see also [24] in this volume), was not enhanced. Given that the ‘N1’ and ‘N2’ components of LEPs partially overlap in time and space, the possibility that the attentional enhancement originates in the N2 activity and spreads into the N1 scalp measurement cannot be ruled out, and would explain the dissociated behavior of N1 and P1. This objection does not apply, however, to the N1 enhancement observed in Nakamura et al.’s [49] report where the two dipolar fields of the magnetic response were simultaneously affected.

Thus, results on attention effects on N1 have been so far only partially consistent, and not devoid of methodological drawbacks. The current state of knowledge indicates that genuine effects of attention upon the opercular N1 may exist, but are of lesser intensity than corresponding effects on the vertex LEP N2. It appears reasonable to consider that general fluctuations of arousal and vigilance do most substantially

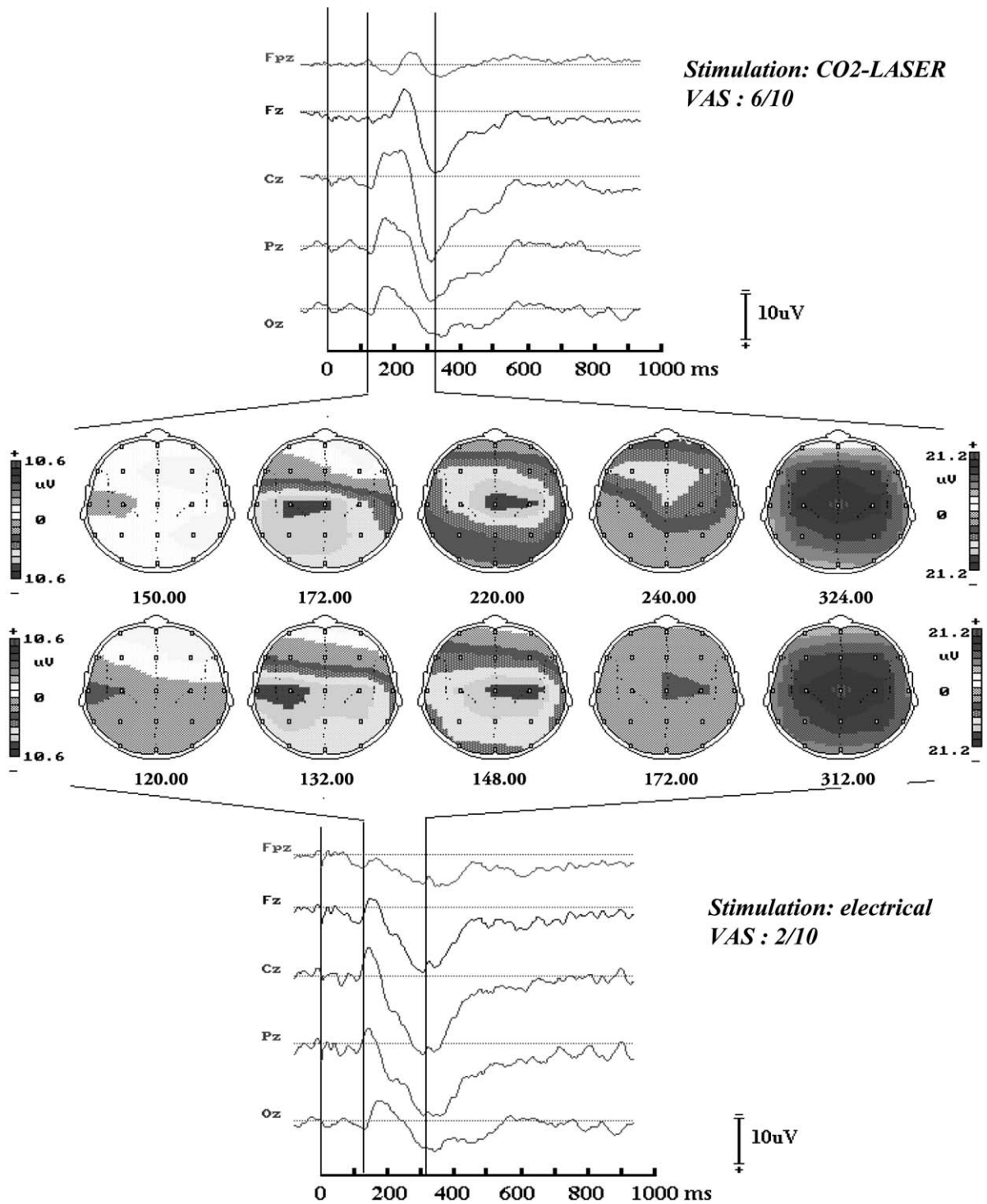


Fig. 1. Scalp responses to painful laser pulses (top) and electrical non-noxious stimulation (bottom) obtained in the same subject. Laser and electrical stimuli were delivered to the same radicular territory (C6) in the right hand. Traces at selected midline electrodes as well as whole-scalp topographic data are shown. Note that in spite of the obvious differences in latency, the overall topography and the internal temporal relationships among components is remarkably similar for both types of stimulation. Such resemblance of scalp topographies suggests similarity of anatomical generators, and the reason why activation of comparable networks may produce such different perceptual experiences as those evoked by noxious laser or non-noxious electrical stimuli remains unclear. Note, however, that laser pulses evoked a frontally distributed negativity (240 ms map) that was absent in case of electrical stimuli, and might have contributed to perceptual differences. A number of responses currently inaccessible to scalp recordings might also differentiate both types of EPs. In addition, changes in the timing and duration of activity within a same anatomical network (and its connected regions) may lead to substantial differences in perception.

affect the LEP N1 wave. In addition to this, the N1 may be sensitive to a more specific ‘sensory gain’ effect, whereby all stimuli of a given modality (in this case thermo-nociceptive) yield enhanced responses when the subject attends to this precise modality (see Näätänen and Picton, 1987 [48] for a discussion on this topic). This kind of effect has been considered to enhance the sensory N1 in both the auditory and the somatosensory modalities (see [22,47,48]), and might underlie the N1 enhancement shown by Lorenz et al. [39] in fibromyalgic patients, which these authors demonstrated not to be due to higher general vigilance levels. The term “hyper-vigilance” sometimes used to describe the sensory disturbance in fibromyalgia is confusing because it actually refers to the liability of these patients to more strongly engage selective attention towards aversive or threatening stimuli rather than to heightened vigilance affecting also neutral stimuli (see also [37]).

One of the greatest difficulties to compare the attentional modulation of the ‘N1’ component of LEP with that of ‘N1’ responses of other stimulus modalities stems from differences in nomenclature. The SEP ‘N1’ response following electrical stimuli is formed by several overlapping components, which have striking similarities with the ‘N1’ and ‘N2’ LEP waves, to the point that, besides latency differences, the dynamics and scalp topography of SEP and LEP sequences are virtually identical [33] (see Fig. 1). Similarly, the attentional effects affecting the AEPs ‘N1’ largely match those reported for both the N1 and N2 LEP waves. Specifically, the N1 in SEPs and AEPs is enhanced by the three parameters that also enhance LEPs N1–N2, namely (a) arousal, (b) sensory gain effects, and (c) selective spatial attention [13,15,22,47,48]. Although attentional changes affected all N1 subcomponents, changes in the SEP ‘vertex N1’ (N140) were in general more important than those in its early-lateralized component (N120) [22,31]. It appears, therefore, reasonable that the set of attentional changes described for the LEP waves N1 and N2 are best described and compared across modalities by considering these two waves as equivalent to the diverse ‘N1’ subcomponents in other modalities. This consideration should also allow (in addition to clarifying aspects of attentional modulation) differentiating the LEP N2 from the cognitive, purely endogenous ‘N2’ wave, which indicates active target detection in any sensory modality [30,31,54,60].

## 8. Conclusion

We reviewed evidence that LEPs represent a series of ERP that significantly depend on attentional and cognitive factors. It allows the view that virtually identical factors modulate the negative (N1, N2) and positive (P2) components of LEP that are known from other stimulus modalities such as audition and vision: (a) arousal and vigilance affecting all components; (b) inter-modal selective attention affecting the N1 and N2 components equivalent to a sensory gain effect; (c) intra-

modal spatial selective attention affecting the N2 (and perhaps N1), equivalent to the presence of a processing negativity; (d) automatic orienting producing a P3a overlapping the P2 component; (e) de novo elicitation of P3b dependent upon contextual task (e.g. oddball) factors involving target detection and memory recall. This composite entity needs to be considered when LEP are experimentally or clinically used in the assessment of sensory and cognitive phenomena and abnormalities of pain sensation. Besides the general requirement to keep attentional and cognitive factors constant across the study variable (e.g. affected versus unaffected dermatomes) future research may specifically address the importance of abnormal attentional modulation by using the appropriate paradigms in order to distinguish organic and psychological manifestations of reduced or enhanced pain perception in distinct diseases. Such approach has already proved useful to differentiate malingering from conversive sensory loss [42].

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