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Electrophysiological correlates of attentional orientation in humans to strong intensity deviant nociceptive stimuli, inside and outside the focus of spatial attention

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Abstract

Laser evoked potentials (LEPs) are electrical brain responses to nociceptive heat stimuli. In a recent study [Legrain, V., Guérit, J.M., Bruyer, R. and Plaghki, L., Pain, 99 (2002) 21-39.], we found that amplitude at ~400 ms was increased by rare intensity deviant nociceptive stimuli (P400 effect). In that study, laser stimuli were randomly delivered on both hands, and subjects were focusing attention on one hand in order to detect rare stimuli. As the P400 effect was found for rare stimuli when spatial attention was directed both towards and away from the stimulated hand, it was postulated to represent a P3a component reflecting an involuntary orientation of attention to unexpected deviant stimuli. However LEPs to strong and weak intensity stimuli were averaged together and some effects could have been underestimated. So, we present a new interpretation of the P400 effect based on separate analyses of strong and weak intensity deviant stimuli. Indeed, the P400 effect was only observed for strong stimuli, and again on both attended and unattended hands. Thus, if the P400 effect reflects P3a, only strong deviant stimuli provided enough signals to induce attentional switching even when they were delivered outside the focus of spatial attention. It is suggested that attentional switching could have been triggered by neural systems having detected sharp increase of intensity. Weak deviant stimuli were not salient enough to induce attentional switching.

Keywords: Pain; Laser evoked potentials; P2; P3a; Involuntary orientation of attention

Laser evoked potentials (LEPs) are brain responses to selective activation of nociceptors by laser-induced heat stimuli and reflect the time-course of nociceptive processes in the brain [3]. The LEP components are also very sensitive to pain-aspecific cognitive factors. For instance, we recently found that N1 and N2 were modulated by the direction of spatial attention to a given body part [10]. This was demonstrated with a sustained selective attention paradigm in which subjects were instructed, during random laser stimulation of both hands, to focus their attention on one hand in order to detect rare changes of intensity. Amplitude in the time-range of P2 was less sensitive to spatial attention, but it was increased by rare intensity deviant stimuli delivered on the hand where attention was focussed on (attended hand), and also on the other hand (unattended hand). This so-called P400 effect was postulated to represent a P3a component reflecting an involuntary switch of attention to new or deviant events, and classically evoked by rare stimuli in the oddball paradigm even when subjects are distracted [4,16,17]. However, rare stimuli were either strong or weak intensity deviant (in comparison to background stimuli), and electrophysiological brain responses to both kinds of stimuli were merged before analysis in order to increase signal/noise ratio in the averaging procedure [10]. At least two effects could not have been noticed. Firstly, as P3a reflects orientation to deviant/novel salient

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event [4,15], strong rare stimuli delivered outside the focus of attention were probably salient enough to involuntary re-attract attention on the unattended hand, but the question remains open concerning weak rare stimuli. Indeed, Näätänen et al. [14] did not find evidence for P3a to rare intensity decrements, while Snyder and Hillyard [16] observed P3a to both louder and softer deviant tones but with much longer interstimulus intervals. P3a elicitation depends on stimulus saliency but also on task constraints [15]. Secondly, it could not be stated whether the P400 effect resulted from P2 amplitude increase or from overlap of P3a in the same time-range. In other words, did attentional switching result from increased neural response in the brain areas generating P2 or from responses in other areas? A recent study showed that rare task-irrelevant nociceptive stimuli could evoke such a modality non-specific component partially overlapped with the laser-evoked P2 [9], which would suggest that rare nociceptive stimuli could capture attention even when they are presented outside the focus of spatial attention, or when they are irrelevant to ongoing activities. In this latter study, two peaks were observed: one common to all kinds of stimuli, and one specific to task-irrelevant rare stimuli [9]. It is possible that the P400 effect reflects overlap of two different responses that were smoothed during averaging strong and weak stimuli together. The present study addresses the question of differential P400 effects for strong and weak intensity deviant laser stimuli.

Nociceptive stimuli (50 ms duration, 80 mm^2 surface area) were randomly delivered by a CO_2 laser (10.6 μm wavelength) on the dorsum of both hands of ten healthy subjects (five men, five women, 26.2 ± 3.6 years). Two intensities were used: 550 mJ (weak stimuli) and 750 mJ (strong stimuli). Subjects were submitted to 32 blocks of 50 stimuli during two sessions. Interstimulus interval was 3 s. Right and left hands were equiprobably stimulated. On each hand, one intensity was frequently presented (80%), the other rarely (20%). Strong stimuli were rare in one half of the blocks, and weak stimuli in the other half. Subjects were instructed to fix the gaze on a central point, to pay attention to stimuli delivered on one hand (attended hand), to count the rare stimuli on that hand, and to ignore the other hand (unattended hand). Right hand was attended during 16 blocks, and left hand during the 16 others (see Ref. [10] for more details).

LEPs were recorded by 19 Ag–AgCl electrodes placed on the scalp according to the 10–20 system, and referenced to linked earlobes (impedance < 5 kΩ). Ground electrode was placed at right wrist, and electrooculogram was recorded by two electrodes placed above and below the right eye. Electroencephalograph (EEG) was recorded with the following parameters: 167 cps sample rate, 3 s time constant, gain of 1000, 0.06–75 Hz band filter, 50 Hz notch filter. EEG epochs (512 point, −500–2566 ms) were digitally filtered (0.1–20 Hz band pass, 48 dB/octave) and baseline corrected (from −500–0 ms), and were averaged according to stimulus intensity, direction of attention, and probability. As, contrary to the early negativities, scalp topography of the positivities was not dependent on the stimulus location, trials to right and left hands were merged together (this was intended to increase the number of epochs in one averaged signal). Amplitude was measured from peak to baseline.

Subjects made more errors when counting weak than strong stimuli (12.5 ± 6.7% vs. 5.1 ± 1.7%; $z = -2.60$, $P = 0.009$). The main positivity was identified at Cz between 350 and 450 ms. Other positivities were looked for at Fz, Cz and Pz. LEP positivity could not be identified for weak stimuli in three subjects. Fig. 1 shows LEPs across midline electrodes. One single peak was identified in the time-range of the P400 effect. A parietal response was evidenced at a much longer latency only for rare attended targets (P600, see Ref. [10]). P400 amplitude and latency were submitted to an ANOVA for repeated measures with the following factors: intensity (strong vs. weak), attention (attended vs. unattended), probability (rare vs. frequent) and electrode (Fz, Cz, Pz).

ANOVA on amplitudes revealed that strong stimuli evoked significantly greater P400 amplitude than weak stimuli ($F_{1,6} = 87.48$, $P < 0.001$). Results showed also significant main effect of electrode ($F_{1,7} = 19.71$, $P = 0.002$) and significant intensity × attention × probability interaction ($F_{1,6} = 12.69$, $P = 0.012$). P400 amplitudes to strong and weak stimuli were submitted to separate ANOVAs. For strong stimuli, P400 amplitude was

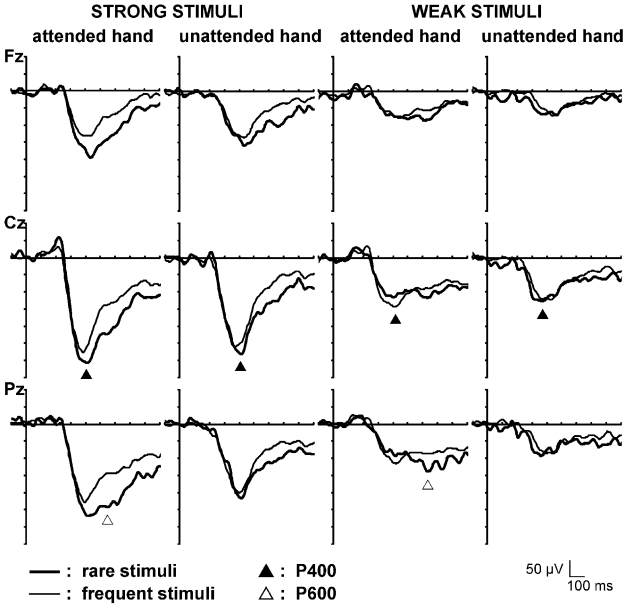

Fig. 1. Grand-mean LEPs across midline electrodes. The main positive peak is seen in each condition at ~400 ms. This P400 effect (▲) was larger in amplitude for rare strong than for frequent strong stimuli, but was not larger for rare weak than for frequent weak stimuli. An additional parietal positivity was evoked at a later latency by both strong and weak attended rare stimuli, that is to-be-counted targets, corresponding to our previous P600 or P3b (△) [10].

larger in the attended than in the unattended condition ($F_{1,9} = 8.59$, $P = 0.017$), and larger for rare than for frequent stimuli ($F_{1,9} = 14.68$, $P = 0.004$) (Fig. 1). These two factors did not interact significantly ($F_{1,9} = 4.20$, $P = 0.071$). Amplitude was the largest at Cz and the lowest at Fz (electrode main effect: $F_{1,12} = 31.58$, $P < 0.001$; all contrasts $P < 0.003$). Maximal amplitude at Cz was confirmed by ANOVA of normalized amplitudes[1] ($F_{1,12} = 32.56$, $P < 0.001$) with no interaction with other factors. For weak stimuli, main effects of attention and probability were not significant ($F_{1,6} = 2.27$, $P = 0.183$; $F_{1,6} = 0.031$, $P = 0.866$). However the interaction between these two factors was significant ($F_{1,6} = 8.52$, $P = 0.027$) as P400 was larger in response to attended than to unattended frequent stimuli ($F_{1,6} = 6.93$, $P = 0.038$), the other comparisons being not significant. P400 to weak stimuli was also larger at Cz ($F_{2,12} = 14.87$, $P = 0.001$; all contrasts $P < 0.004$), and this was again confirmed with normalized amplitudes ($F_{2,12} = 15.17$, $P = 0.001$). ANOVA on latencies showed a significant main effect of probability ($F_{1,6} = 6.15$, $P = 0.048$) as P400 was later for rare than for frequent stimuli. Attention had no significant effect ($F_{1,6} = 0.90$, $P = 0.380$). As the probability effect on P400 amplitude was significant in the strong but not in the weak intensity condition, latencies were also submitted to two separates analyses. The probability main effect on latencies was still significant for strong ($F_{1,9} = 10.33$, $P = 0.011$) but not for weak stimuli ($F_{1,6} = 2.59$, $P = 0.159$).

We confirmed that, in a sustained selective attention task, LEP amplitude was increased in the P2 time-range by rare nociceptive stimuli. However this effect was observed when deviant stimuli were stronger, but not weaker, than the background frequent stimuli. For strong stimuli, amplitude increase was observed for both attended and unattended stimuli.

We had proposed that the P400 effect could represent a P3a component reflecting an involuntary switch of attention to new/deviant stimuli [4]. In a sustained selective attention task, Woods [19] observed auditory P3a in the unattended channel only by novel stimuli (complex sounds and noises) and not by frequency deviant stimuli. These novel sounds produced greater reaction times to subsequent targets. Yamaguchi and Knight [20] found larger P3a to irrelevant electrical shocks than to irrelevant mechanical taps when subjects were discriminating mechanical taps delivered on other fingers. It means that novel sounds and electrical shocks were more salient to induce orientation or re-orientation of attention [4,6,15]. In our task, strong deviant stimuli, although not novel, were probably also salient enough to evoke P3a, even when they were presented outside the focus of spatial attention. Selective spatial attention increases N1–N2 amplitudes at an earlier latency when the stimulated hand was actively attended [10]. As the P400 effect was seen for unattended rare strong stimuli, these stimuli could evoke a P3a-like response reflecting a re-allocation of attention although they were firstly gated by early selective operations as reflected by lower N1–N2 amplitudes. The P400 effect was not significant for unattended rare weak stimuli; it was also not significant for attended rare weak targets, although a P600 (or P3b) was present [10]. They were probably not salient enough to produce P3a. Attentional switching is supposed to be triggered by signals from early neural mechanisms involved in transient-detection and change-detection operations [13,16]. In auditory processing, the former ones seem to initiate orientation to new fresh neural inputs and are indexed by N1 subcomponents, while the latter ones register changes in homogeneous stimulus sequences and are expressed by mismatch negativity (MMN) components. Auditory MMNs are evoked by any change of regularities including intensity decrement [5,14]. The P400 effect was only seen for strong deviant stimuli. This implies that, if similar systems exist for somatosensory processes, attentional switch to deviant nociceptive stimuli was probably triggered mainly by transient-detector systems having detected sudden sharp increase in stimulus intensity [4,5]. This function could be subserved by SII areas that were recently shown to have some kind of 'all-or-none responses' to painful laser stimuli [18]. However N1 and N2, suggested to be generated in SII [7], were not significantly modulated by rare stimuli [10]. An alternative explanation would be that attentional switching to rare weak stimuli was less effective because counting weaker stimuli was more difficult [4,15], as supported by behavioural data.

The issue whether P2 shares some mechanisms with P3a or whether distinct P3a-like components were evoked by the present experimental manipulation during the same time-range remains open. As in the previous study [10], our results revealed only one peak in the range of the P400 effect, which had the same waveform and topography across conditions. For strong stimuli, the P400 latency was longer for rare than for frequent stimuli. However the latency difference is not enough to conclude for an overlap of two distinct components. In another study [9], we found that task-irrelevant rare nociceptive stimuli evoked a positivity with two peaks, at 360 ms and at 460 ms. However this was found in a 3-stimulus oddball paradigm classically evoking the novelty-P3, a complex P3 wave mainly but not only composed by P3a [6]. Moreover, P3a itself is made up of different subcomponents [4]. It must also be noted that both P3a and laser-evoked P2 are, at least partially, generated in the anterior cingulate gyrus [1,11].

Finally we found that spatial attention had an effect on P400 amplitude in response to strong stimuli. P400

[1] For each condition, each subject's raw amplitude was divided by the square root of the sum of the squared mean amplitudes from each electrode. This transformation was intended for circumventing the fundamental incompability between the additive ANOVA model and the multiplicative effect on evoked potential voltages produced by changes in sources strength, and provides best statistical estimators of difference in scalp topography between experimental conditions [12].

modulation by spatial attention is in accordance with amplitude decrease of the laser-evoked P2 when subjects are distracted from the nociceptive stimuli [2,3,8] and with the sensitivity of P3a to the attentional set of the task [4,15]. Woods [19] also found larger amplitudes for novel sounds on the attended than the unattended ear.

In conclusion, it was shown that strong intensity deviant nociceptive stimuli elicited LEP amplitude increase, probably reflecting P3a-like mechanisms, as did very salient novel sounds. If correct, we propose that this P400 effect could be a neurophysiological basis to understand how painful events capture attention and disrupt current activities in order to rapidly process a potential source of danger. Further investigations are needed in order to show that P400 effect-eliciting nociceptive stimuli also produce behavioural consequences of attentional switching, that is, distraction.

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