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Single-trial detection of human brain responses evoked by laser activation of Aδ-nociceptors using the wavelet transform of EEG epochs☆

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Abstract

The aim of this study was to identify EEG changes induced by Aδ-nociceptor activation in single trials. In a preliminary experiment, intense CO_2 laser stimuli were delivered to the hand dorsum of five volunteers. The average amplitude of EEG epochs was estimated in the time-frequency (TF) domain using the continuous Morlet wavelet transform (CMT). The result was used as a TF filter enhancing Aδ-nociceptor induced EEG responses. In a second experiment, eight other subjects were delivered laser stimuli with six intensities. The CMT of each EEG epoch was computed. After applying the TF filter, amplitudes within a predefined interval were summed. Whether this sum predicted the occurrence of Aδ-nociceptor activation was tested using the reaction-time to discriminate between Aδ- or C-fibre mediated detection. Results showed that this method accurately identified single-trial EEG responses to Aδ-nociceptor activation.

Keywords: Laser-evoked potentials; Wavelet analysis; Single-trial event-related potentials; Aδ-fibres

Brief and powerful CO_2 laser heat stimuli may produce a characteristic dual sensation composed of first and second pain [5]. Several studies have shown that these two perceptual responses are respectively related to the activation of Aδ- and C-fibre nociceptors [1,9]. As the activation threshold of C-nociceptors is lower than that of Aδ-nociceptors [14], laser stimuli of low power selectively activate C-nociceptors while laser stimuli of high power quasi-simultaneously activate both Aδ- and C-nociceptors. However, as the conduction velocity of Aδ-fibres (± 10 m/s) is much greater than that of C-fibres (± 1 m/s), the sensation of second pain is delayed relative to that of first pain, depending on the peripheral conduction distance [2,8]. The reaction-time (RT) to the first sensation felt may thus be used to determine whether stimulus detection was mediated by Aδ- or C-nociceptor inputs [13].

With high stimulus intensity, laser-evoked brain potentials (LEP) display components in a time-window compatible with the conduction velocity of Aδ-fibres (± 160–390 ms) [1]. Several studies showed that this late LEP is a correlate of first pain (for a review see Ref. [3]). The aim of the present study was to detect these EEG responses in single trials. As the signal is embedded in the ongoing EEG with a low signal-to-noise ratio (SNR), a new method, based on the time-frequency (TF) wavelet decomposition of EEG epochs, was developed. It was assumed that decomposing epochs in both time and frequency would allow disentangling of stimulus-locked and frequency-steady EEG changes from background EEG and non-cerebral artefacts. As further described, the TF filter used to enhance single-trial EEG responses was electrophysiologically determined in a preliminary recording session. The method yielded, for each single EEG epoch, an 'EEG response value' (ERV) hypothesized to predict the presence or absence of electrophysiological correlates of Aδ-nociceptor activation. This hypothesis was tested in a second recording session where RT measures were used to indicate the perception of Aδ-fibre-related first pain.

In both recording sessions, CO_2 laser heat stimuli (duration: 50 ms; beam diameter: 10 mm; ISI: 30–40 s;

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see Ref. [6] for details) were applied to the left hand dorsum. Sessions were subdivided into four successive blocks, each consisting of 30 stimuli. Five volunteers (aged 28 ± 9 years) participated in the preliminary recording session. Three intensities (4.3, 7.3 and 10.9 mJ/mm^2) were applied in random order and equal probability. In this session, besides paying attention to the upcoming stimulus, subjects were assigned no task. Eight other volunteers (aged 28 ± 8 years) participated in the second recording session. Six different intensities ranging from 3.4 to 10.9 mJ/mm^2 were applied in random order and equal probability. In this session, RTs were obtained by asking subjects to press, at first sensation felt, a button held in the right hand.

EEG epochs (−500 to 2500 ms) were sampled at 256 cps from C_Z vs. A_1A_2 (PL-EEG, Walter Graphtek, Germany; gain: 1000; filter: 0.06–75 Hz). Recording electrode C_Z was chosen as prominent components of LEP are maximal at the vertex (for a review see Ref. [3]). Two electrodes placed at the upper left and lower right side of the right eye monitored ocular movements. After baseline correction (reference interval −500 to 0 ms), sweeps contaminated by EOG were rejected by visual inspection (469 and 693 trials remaining in sessions 1 and 2, respectively). A TF representation of each single EEG epoch was performed using the continuous Morlet wavelet transform (CMT). The spread of the Morlet function was set to $2.5/\pi\omega_0$ (ω_0 being the average frequency of the mother wavelet). Explored frequencies ranged from 1 to 15 Hz in steps of 0.24 Hz. The modulus of the transform expressed oscillation amplitude as a function of time and frequency. Details of the procedure can be found in Ref. [6].

Recordings of the preliminary session were used to produce a weighted TF filter (W) identifying the TF distribution of EEG changes induced by Aδ-nociceptor activation. To produce this TF filter, only supra-threshold high stimulus intensity (10.9 mJ/mm^2; $n = 127$) trials were used. The filter was computed by averaging the CMT of these trials. The result was normalized using, for each frequency row, the average of amplitudes enclosed in the foreperiod between −400 and −100 ms (ERD% as defined by Pfurtscheller [7]). The result expresses the average relative increase or decrease of oscillation amplitude as a function of time and frequency (Fig. 1: W). As amplitudes were averaged regardless of phase, this procedure enhanced stimulus-related EEG changes both phase-locked (i.e. event-related potentials) and non-phase-locked (i.e. event-related synchronization and desynchronization) to stimulus onset [11].

Each CMT of the second recording session was normalized (reference interval −400 to −100 ms; ERD%). The result expresses, for each single EEG epoch, the relative increase or decrease of oscillation amplitude (Fig. 1: CMT_i: one epoch shown as an example). CMT_i was then multiplied by the previously computed weighting matrix W (Fig. 1: $W{\cdot}CMT_i$). This operation can be considered as applying a TF filter to the single-trial data. Finally, the sum of TF cells ranging from 0 to 700 ms was calculated. It was hypothesized that this ERV would allow identification of the presence or absence of electrophysiological correlates of Aδ-nociceptor activation.

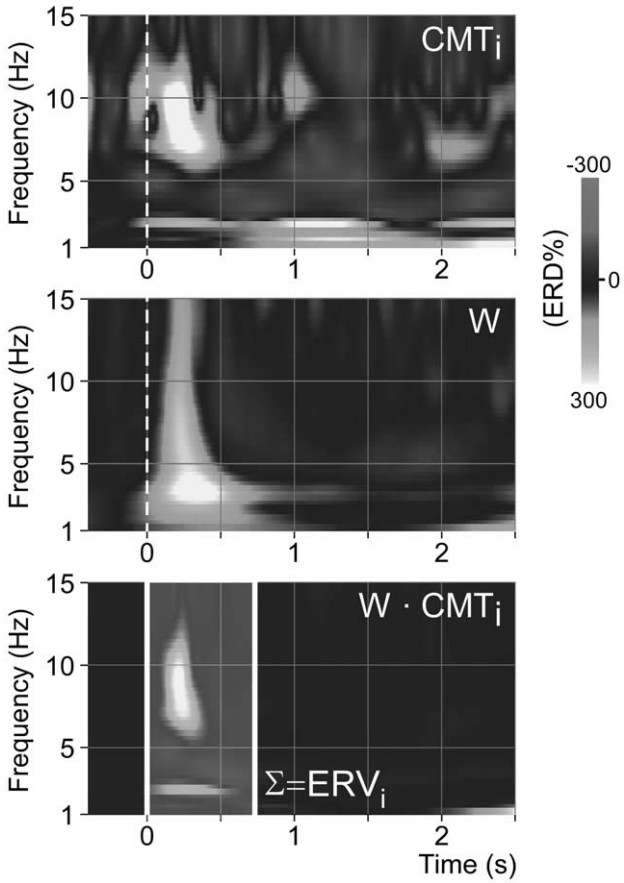

Fig. 1. The modulus of the CMT was used to express EEG oscillation amplitude as a function of time and frequency. In a preliminary recording session (five subjects), supra-threshold high intensity heat stimuli (10.9 mJ/mm^2; $n = 127$) were used to produce an electrophysiologically determined weighted TF filter identifying EEG changes induced by Aδ-nociceptor activation (W). To compute W, CMTs were averaged and normalized such as to express the average relative change of oscillation amplitude (ERD%) as compared to a reference interval defined in the foreperiod (−400 to −100 ms). Eight subjects participated in a second recording session. In this session, the normalized CMT of each single EEG epoch (CMT_i: one epoch shown as an example) was computed and then filtered by computing the product of W and CMT_i ($W{\cdot}CMT_i$). This operation filtered-out EEG fluctuations not occurring at the latency and frequency of event-related EEG responses. Finally, the sum of TF cells ranging from 0 to 700 ms was calculated. It was hypothesized that this ERV, computed for each single EEG epoch, would allow identification of the presence or absence of electrophysiological correlates of Aδ-nociceptor activation.

At the lowest stimulus intensity, only 15% of trials were detected. At these and at intermediate intensities, subjects frequently described the stimulus as a sensation of diffuse warmth. At higher intensities, subjects often reported an additional sharp pricking sensation. As expected, the frequency distribution of RTs was bimodal [2,8]. A cut-off of 650 ms optimally discriminated two groups of RTs labelled 'Late RT' (RT ≤ 650 ms) and 'Ultra-late RT' (RT > 650 ms). The proportion of Late RTs clearly increased with the intensity of the stimulus (Fig. 2B). As

explained above, Late RT trials were considered as trials where detection was mediated by Aδ-nociceptor activation while Ultra-late RT trials were considered as trials where detection was mediated by selective C-nociceptor activation. This classification was used to estimate (1) the absolute detection threshold and (2) the 'first pain' detection threshold. Fig. 2B displays both probability of detection curves as a function of stimulus intensity. The absolute detection threshold was 4.1 ± 0.8 mJ/mm^2. The detection threshold for 'first pain' was 7.8 ± 0.9 mJ/mm^2.

To estimate the discrimination performance of the ERV, a receiver operating characteristic (ROC) curve was plotted using RT to define the state of each trial (Fig. 2A). Late RT trials ($n = 191$) were compared to trials with no detection ($n = 191$). The area under the curve (θ) was 0.800 ± 0.023, demonstrating a good discriminative performance. A single decision criterion (β), common to all subjects, was selected such that specificity (0.76 ± 0.11) equalled sensitivity (0.74 ± 0.09). Consequently, false positive and negative results should not have biased the estimation of threshold. The probability of ERV exceeding β was plotted as a function of stimulus intensity (Fig. 2B). Using this method, the estimated 'electrophysiological threshold' of brain responses elicited by Aδ-nociceptor activation was 7.2 ± 1.5 mJ/mm^2. This result was very similar to the psychophysical threshold of first pain. Paired-sample Wilcoxon comparison between both estimated thresholds did not reveal a difference ($P = 0.104$). Most probably due to false positive and negative results, the slope of the ERV probability of the detection curve was not as steep as that of the psychophysical threshold.

The additive-noise model considers that each single EEG epoch is the sum of (1) EEG changes induced by the event, (2) background EEG and (3) non-cerebral artefacts [10]. As the SNR of event-related EEG changes is small, very few studies have attempted to study EEG responses in single trials [4,12]. In this study, TF decomposition of EEG epochs was used to enhance the single-trial SNR. Indeed, background EEG and non-cerebral EEG artefacts should be randomly distributed in the time-domain (i.e. not time-locked to the event onset). Furthermore, the frequency distribution of at least part of these contributions should differ from that of event-related EEG responses. TF decomposition of EEG epochs should thus allow a better dissociation of event-related responses from 'noise'. In addition, as this method was based on averaging oscillation amplitude across EEG epochs, it enhanced the SNR of both phase-locked and non-phase-locked event-related EEG changes. Taking into account both types of EEG activities may have contributed to increasing the method performance. The TF matrix (W) can be considered as an electrophysiologically determined weighted TF filter. Near-zero weights correspond to TF localities where the studied event did not induce important changes in EEG amplitude while positive or negative weights correspond to TF localities where the studied event induced either an

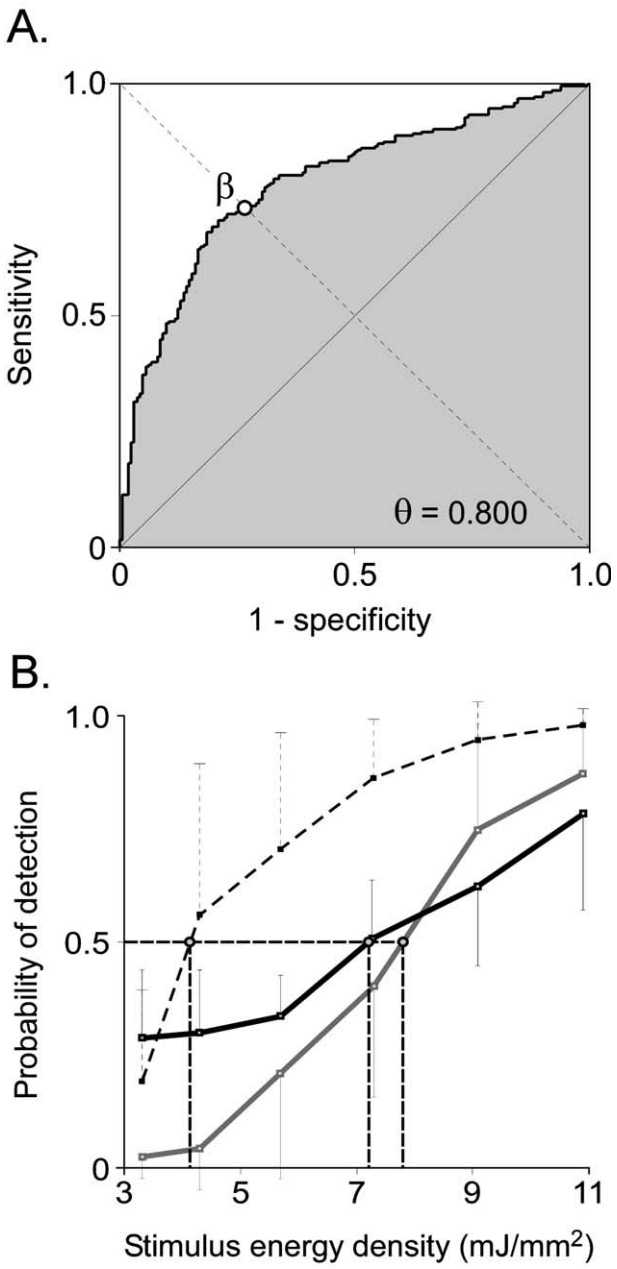

Fig. 2. (A) Receiver operating characteristic (ROC) curve assessing the discriminatory performance of the ERV computed for each single EEG epoch. RT was used to define the state of each trial. Late RT trials (RT ≤ 650 ms; $n = 191$), considered as trials where detection was mediated by Aδ-nociceptor activation, were compared to undetected trials ($n = 191$). The area under the curve (θ), an index of discriminatory performance, was 0.800 ± 0.023 and significantly ($P < 0.0001$) greater than 0.5 (no predictive value). A decision criterion (β) was chosen such that specificity (0.76 ± 011) equalled sensitivity (0.74 ± 0.09). (B) Probability of detection curves as a function of stimulus intensity (six different intensities ranging from 3.4 to 10.9 mJ/mm^2). The absolute probability of detection is plotted as a dashed line. The probability of detecting the stimulus with a Late RT (compatible with the perception of first pain) is plotted as a light grey line. The probability that ERV exceeded the decision criterion (β) is plotted as a thick black line. Error bars quantify the standard deviation across subjects. Curves were used to estimate the absolute detection threshold (4.1 ± 0.8 mJ/mm^2), the psychophysical threshold of first pain (7.8 ± 0.9 mJ/mm^2) and the electrophysiological threshold of Aδ-fibre-related EEG responses (7.2 ± 1.5 mJ/mm^2) for $P = 0.5$.

increase or a decrease of oscillation amplitude (Fig. 1: W). Applying this TF filter to single EEG epochs should thus allow filtering of EEG fluctuations not occurring at the latency and frequency of event-related responses. The RT task performed by subjects in the second recording session most probably induced additional motor-related EEG changes. However, as subjects participating in the preliminary recording session did not perform a motor task, it can be expected that the thereby computed TF filter selectively enhanced EEG changes related to the stimulus and not to the additional RT task. In addition, computation of W was entirely independent of the main recording session as these subjects did not participate in the preliminary recording session. Computing ERV allowed quantification of the correlation between W and each single EEG epoch (CMT_i). Indeed, while amplitude changes occurring at near-zero weighted TF localities did not significantly modify the ERV, amplitude changes occurring at heavily weighted TF localities strongly influenced the ERV. Negative correlation reduced the ERV while positive correlation increased the ERV. This quantification allowed an accurate detection of trials where event-related responses were expected.

In a recent study, Jung et al. [4] attempted to examine event-related EEG responses in single trials using independent component analysis (ICA) to perform blind source separation of multi-channel EEG recordings. This method is based on the assumption that each EEG sample consists of a different combination of spatially fixed sources projected onto the scalp sensors. ICA allows unmixing of the EEG recording into components hypothesized to reflect these sources. Their study showed that this method increased the SNR of single-trial EEG responses. Combining both methods could allow further denoising of single EEG epochs.

As ERV allows assessment of the presence or absence of event-related EEG responses in single trials, this electrophysiological index could be used to concurrently examine behavioural variables and event-related EEG changes. Access to the single-trial dynamics of these electrophysiological responses could reveal information that is spread out when averaging a large number of trials.

The EEG response to Aδ-nociceptor activation may be decomposed into several components each displaying a distinct latency, frequency distribution, and scalp topography. In the present study, all these components were confounded in the computation of the ERV. However, in future studies, distinct ERVs may be computed by defining TF regions circumscribing each individual component of the response.

Applied to LEP, this method accurately identified single-trial EEG changes related to the cortical processing of Aδ nociceptive information. The activation threshold of this electrophysiological correlate was not significantly different from the psychophysical threshold of first pain. Not only could the electrophysiological threshold of Aδ-nociceptor activation be used to estimate thresholds in subjects unable to communicate their perception (i.e. children, mentally disabled, etc.) but comparison of both thresholds could, in some cases, provide useful information both in clinical evaluation and research.

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