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The measure of randomness by leave-one-out prediction error in the analysis of EEG after laser painful stimulation in healthy subjects and migraine patients

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Abstract

Objective: We aimed to perform a quantitative analysis of event-related modulation of EEG activity, resulting from a not-warned and a warned paradigm of painful laser stimulation, in migraine patients and controls, by the use of a novel analysis, based upon a parametric approach to measure predictability of short and noisy time series.

Methods: Ten migraine patients were evaluated during the not-symptomatic phase and compared to seven age and sex matched controls. The dorsum of the right hand and the right supraorbital zone were stimulated by a painful CO_2 laser, in presence or in absence of a visual warning stimulus. An analysis time of 1 s after the stimulus was submitted to a time–frequency analysis by a complex Morlet wavelet and to a cross-correlation analysis, in order to detect the development of EEG changes and the most activated cortical regions. A parametric approach to measure predictability of short and noisy time series was applied, where time series were modeled by leave-one-out (LOO) error.

Results: The averaged laser-evoked potentials features were similar between the two groups in the alerted and not alerted condition. A strong reset of the beta rhythms after the painful stimuli was seen for three groups of electrodes along the midline in patients and controls: the predictability of the series induced by the laser stimulus changed very differently in controls and patients. The separation was more evident after the warning signal, leading to a separation with *P*-values of 0.0046 for both the hand and the face.

Discussion: As painful stimulus causes organization of the local activity in cortex, EEG series become more predictable after stimulation. This phenomenon was less evident in migraine, as a sign of an inadequate cortical reactivity to pain.

Significance: The LOO method enabled to show in migraine subtle changes in the cortical response to pain.

Keywords: EEG analysis; Migraine; Laser stimulation

1. Introduction

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. (Lorenz and Garcia-Larrea, 2003). Attention and distraction in turn reduce or enhance the activation of cortical areas devoted to pain elaboration, which is expressed by LEPs amplitude. Event-related modulation of EEG spectral energy is another measure of cortical activation, which has been demonstrated during multiple behaviors

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including movement (Crone et al., 1998; Ohara et al., 2000a), vision (Tallon-Baudry et al., 1996), audition (Crone et al., 2001a), and language (Crone et al., 2001b). In a previous study, wavelet time–frequency analysis and bandpass filtering was employed to test Event-related desinchronization (ERD) quantitatively in subdural electrocorticographic recordings while subjects either attended to, or were distracted from, a painful cutaneous laser stimulus. (Ohara et al., 2004). In all subjects, ERD was more widespread and intense during attention to laser stimuli than during distraction from the stimuli.

Several LEPs studies have showed an abnormal pattern of cortical activation under painful stimuli in migraine patients, consisting of reduced habituation to repetitive stimuli (de Tommaso et al., 2005; Valeriani et al., 2003) and reduced inhibitory effect of distraction (de Tommaso et al., 2003): LEPs amplitude was employed as measure of variation between different states of attention, even if the occurrence of artefacts may reduce the clearness of the peaks, limiting the detection of subtle modifications.

The EEG time–frequency wavelet analysis, is a valid method to show the development of EEG frequencies modifications after painful stimuli, according to Ohara et al. (2004). In addition, other methods may be employed in order to detect the modifications induced by laser stimuli on EEG activity in migraine patients: in this study, we performed a novel analysis, based upon a cross-trial correlation task, in order to select the most activated cortical regions, followed by a parametric approach to measure predictability of short and noisy time series, used to quantify predictability (Vapnik and Vapnik, 1998). This approach has already been used in Ancona et al. (2005) to analyse systolic arterial pressure time series from healthy subjects and chronic heart failure patients.

The basic idea in this approach is that different physiological states may be characterized in terms of predictability of time series. The predictability is connected to the complexity of the series itself, resulting from complicated regulation mechanisms: here, we extend and elaborate previous findings showing its applicability in the analysis of EEG activity evoked by CO_2 laser painful stimulation.

In the present study, we aimed to perform a quantitative analysis of event-related modulation of EEG activity, resulting from a not-warned and a warned paradigm of painful laser stimulation, in order to detect subtle modifications of cortical activity in migraine patients. We choose to test only the properties of sustained attention to laser stimuli, without performing any contemporary distraction task, which may cause activation of several cortical areas during EEG recording.

2. Materials and methods

2.1. Subjects

Ten patients suffering from migraine without aura (Headache Classification Committee, 2004) were submitted to CO_2 laser stimulation, during the not-symptomatic phase. They were seven females and three males, aged 23–40. (mean age 30.1 + 6.9) All patients were diagnosed after six months' follow-up. Patients with general medical, neurological, or psychiatric diseases, and patients who were taking psycho-active drugs, or prophylactic treatment for headache, or who were assessed as overusing analgesic drugs in the last 2 months, were excluded from the study. All patients were evaluated at least 72 h after the end of the critical migraine phase (mean 75 + 2.1 h) and well before the next attack (mean 48 + 8.2 h), verified by the headache diary during a following clinical examination. Seven sex and age matched healthy subjects were also submitted to the experimental procedure (five females and two males, aged 22–41—mean 30.3 + 5.5).

The experiment was undertaken with the understanding and written consent of each subject and with the ethical approval of the Neurological and Psychiatric Department of Bari University.

2.2. Laser stimulation paradigm

CO_2 laser stimulation was delivered on the skin of the dorsum of the right hand and the right supraorbital zone. The pain stimulus was laser pulses (wavelength 10.6 μm) generated by a CO_2 laser (Neurolas, Electronic Engineering, Florence, Italy; www.elengroup.com). The beam diameter was 2.5 mm, and the duration of the stimulus pulse was 25 ms. We used a fixed intensity set at 7.5 W for both the hand and the supraorbital zone (Bihel et al., 1984). For each site of stimulation, 40 laser stimuli were delivered. A series of 20 stimuli was delivered without any warning signal and a random ISI, ranging from 10 to 20 s: in another series, all stimuli were preceded by a warning flash, followed by a fix interval of 3 s, after which the painful stimulation occurred. In each series of stimulation, subjects were requested to count the stimuli. The sequence of warned and not-warned tasks in the two sites of stimulation was randomly assigned in all cases. Subjects were requested to rate the intensity of painful stimuli at the end of the warned and the unattended trials, using a 0–100 VAS.

2.3. Data acquisition

Signals were recorded through 19 disk electrodes, according to the 10–20 international system (impedance below 5000 Ω), referring to the nasion with the ground at Fpz. Signals were amplified and stored on a biopotential analyzer at a sampling rate of 256 Hz. (MICROMED