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EXPECTATION TO FEEL MORE PAIN DISRUPTS THE HABITUATION OF LASER-PAIN RATING AND LASER-EVOKED POTENTIAL AMPLITUDES

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Abstract—Increased pain perception due to the expectation to feel more pain is called nocebo effect. The present study aimed at investigating whether: (1) the mere expectation to feel more pain after the administration of an inert drug can affect the laser-pain rating and the laser-evoked potential (LEP) amplitude, and (2) the learning potentiates the nocebo effect. Eighteen healthy volunteers were told that an inert cream, applied on the right hand, would increase the laser pain and LEP amplitude to right hand stimulation. They were randomly assigned to either ''verbal session'' or ''conditioning session''. In the ''verbal session'', LEPs to both right and left hand stimulation were recorded at the same intensity before (baseline) and after cream application. In the ''conditioning session'', after an initial cream application the laser stimulus intensity was increased surreptitiously to make the subjects believe that the treatment really increased the pain sensation. Then, the cream was reapplied, and LEPs were recorded at the same stimulus intensity as at the baseline. It was found that the verbal suggestion to feel more pain disrupted the physiological habituation of the laser-pain rating and LEP amplitude to treated (right) hand stimulation. Unlike previously demonstrated for the placebo effect, the learning did not potentiate the nocebo effect.

Key words: nocebo, learning, verbal suggestion, laser-evoked potentials.

INTRODUCTION

Pain is a multidimensional sensory experience, including a perceptive/discriminative aspect and an emotional/affective component. Beyond the characteristics of the painful stimulus, the pain perception is influenced also by the environmental and psychological context in which the subject is feeling pain. When the context reduces the perceived pain intensity, we speak of ''placebo effect'', while in case of increased pain intensity perception, the term ''nocebo effect'' is used (Benedetti et al., 2007). Although less studied than placebo, the occurrence of nocebo effect has been investigated in experimental (Benedetti et al., 2003; Colloca et al., 2010; van Laarhoven et al., 2011) and clinical conditions (Vlaeyen and Linton, 2000; Lorber et al., 2007). What emerges from the literature is that expectation plays a key role in inducing a nocebo effect (Lorenz et al., 2005; Keltner et al., 2006), and influences the effect of a pharmacological therapy (Bingel et al., 2011). As placebo, also the nocebo effect does not need consciousness and can be induced by unconscious cues (Jensen et al., 2012).

The most reliable laboratory tool for assessing the nociceptive pathway function is laser-evoked potentials (LEPs) (Haanpää et al., 2011; Valeriani et al., 2012). LEPs are related to the activation of type II AMH mechanothermal nociceptors. The afferent volley is conducted along the small myelinated (Aδ) primary sensory neurons and the spino-thalamic pathway (Bromm and Treede, 1991). LEPs consist of a temporal lateralized component (N1), followed by a larger vertex biphasic potential reaching its maximal amplitude on the Cz vertex (N2/P2). While the N1 is probably generated in the opercular (SII/insula) area, the N2 and P2 potentials receive the largest contribution from the anterior cingulate cortex (Garcia-Larrea et al., 2003). Previous studies showed that LEP amplitude reduction does represent an objective measure of the placebo effect (Wager et al., 2006; Watson et al., 2007; Colloca et al., 2008b). Colloca and colleagues investigated the effect of the mere verbal suggestion and learning on LEPs, and found that the exposure to a prior experience is able to determine a stronger placebo effect, both at behavioral and neurophysiological levels (Colloca et al., 2008b), thus concluding that learning potentiates the placebo effect.

As for the nocebo effect, there are two studies showing that a preconditioning cue can increase the LEP amplitude (Lorenz et al., 2005; de Tommaso et al., 2012); however, only the verbal suggestion was considered, while a possible effect of learning was not explored.

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Abbreviations: LEP, laser-evoked potential; VAS, visual analogue scale.

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Moreover, no previous study investigated the effect on LEP amplitude of the administration of an inert substance, which the subject was led into thinking would increase the pain perception (‘‘nocebo drug”).

The aims of the present study were to investigate whether: (1) the mere expectation to feel more pain after the administration of a ‘‘nocebo drug” can affect the laser-pain rating and the LEP amplitude, and (2) the learning potentiates the nocebo effect, as it does with the placebo effect.

EXPERIMENTAL PROCEDURES

Subjects

Eighteen right-handed healthy volunteers were enrolled in our neurophysiological laboratory (10 male, eight female, mean age: 29 ± 5 years, range 21–40 years). They were randomly assigned to one of two different experimental protocols, named ‘‘verbal session” (nine subjects: mean age 29 years, range: 23–40 years, three females, six males) and ‘‘conditioning session” (nine subjects: mean age 28 years, range: 21–34 years, five females, four males), in which the effect of the mere verbal suggestion and that of the verbal suggestion + learning were investigated, respectively. Subjects were excluded in case of symptoms or signs of focal upper limb entrapment, cervicobrachialgia, polyneuropathy or history of headache. The study protocol was approved by the local Ethics Committee; all participants signed an informed consent form to participate in the study, and could interrupt the experiment at any time.

Laser stimulation and LEP recording

Laser pulses (wavelength, 1.34 μm) were delivered by a YAP Stimul 1340 (Electronic Engineering, Florence, Italy). Laser stimulus intensity was fixed at 38 mJ/mm^2, which was perceived by all subjects as a painful pinprick (Valeriani et al., 2002; Cruccu et al., 2003). The interstimulus interval was 10 s. LEPs were recorded using the 32 EEG scalp electrodes (according to the 10–20 International System). The reference electrode was placed at the nose, and the ground on the forehead (Fpz). Eye movements and eye blinks were monitored by an electrooculographic (EOG) electrode located above the right eyebrow. Signals were amplified and filtered (bandpass 0.3–70 Hz). The analysis time was 1000 ms with a bin width of 2 ms. In our subjects, averages of 25–30 trials were recorded for each stimulation site. However, we kept the number of trials of each average constant in the same subject. In order to ensure that the attention level of our subjects did not change across the whole experiment, they were asked to count the number of the received laser stimuli silently. Averages with a percentage of mistakes higher than 10% were discarded.

Study design

Nocebo effect was obtained by applying an inert cream (with no color and no smell) on the dorsum of the right hand. The subjects were told that the cream was derived from red hot chili peppers and would increase their own pain sensation due to laser pulses. In order to avoid possible effects of the cream per se on heat conductance, after 5 min the cream was accurately removed. Note that the examiner who gave the information to the subjects always wore gloves when manipulating the cream. The cream-treated skin area was not different from the stimulated area.

In all subjects, we recorded initial LEP averages to both left and right hand stimulation in order to accustom our subjects to the painful laser pulses. These recordings were not considered in the statistical analysis. Then, baseline LEPs were recorded to both left and right hand stimulation in counterbalanced order across subjects.

In the ‘‘verbal session”, the cream was applied after the baseline recordings and kept on the skin for 5 min. Then, the cream was removed and LEPs (‘‘after drug” LEPs) were recorded first to right and then to left hand stimulation. In the ‘‘conditioning session”, the cream was applied after the baseline recordings and kept on the skin for 5 min. Then right hand LEPs were recorded after having increased the laser pulse intensity by 10 mJ/mm^2 surreptitiously, in order to convince the subject that the cream did increase the laser-pain intensity. This recording was obtained using the same parameters as all other recordings (see above) and was not used for the statistical analysis of the ‘‘nocebo effect”. However, it was compared to the baseline LEPs, in order to demonstrate an intensity-dependent increase of the LEP amplitudes. After this LEP recording, lasting about 5 min, the cream was applied again and kept on the skin for 5 min. Subjects were told that this second application was performed to evaluate the reliability of the experiment. Then, right hand ‘‘after drug” LEPs were recorded after having reduced the stimulation intensity to that used for the baseline. Lastly, ‘‘after drug” LEPs were recorded to left hand stimulation (Fig. 1). In summary, six and seven averages were recorded in verbal session and conditioning session, respectively. Moreover, since in both ‘‘verbal” and ‘‘conditioning” sessions the subjects were told that the inert cream would increase the laser-pain perception, we could assume that in ‘‘verbal session” there would be a mere verbal suggestion, while in the ‘‘conditioning session” a learning process would be added to the verbal suggestion.

The subjects reported their laser pain rating at the end of each LEP recording according to a visual analogue scale (VAS) ranging from 0 = no painful sensation to 100 = worst imaginable pain.

LEP components and statistical analysis

The same author (R.G.), blinded to the purpose of the study, measured LEP latencies and amplitudes, and performed the statistical analysis.

Peak latencies of all the main LEP components (N1, N2, and P2 potentials) were measured. N1 amplitude was calculated by referring the contralateral T3/T4 electrode to the Fz lead off-line (Kunde and Treede, 1993). The peak-to-peak N2/P2 amplitude was measured