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Expectation of nocebo hyperalgesia affects EEG alpha-activity

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ABSTRACT

Changes in EEG activity have been related to clinical and experimental pain. Expectation of a negative outcome can lead to pain enhancement (nocebo hyperalgesia) and can alter the response to therapeutic interventions. The present study characterizes EEG alteration related to pain facilitation by nocebo. Thirty healthy subjects were randomly assigned to the nocebo or control group. Five-minute EEG was recorded under: resting state, tonic innocuous heat and tonic noxious heat before and after the application of a sham inert cream to the non-dominant volar forearm combined with cognitive manipulation. The intensity and unpleasantness of heat-induced pain increased after cognitive manipulation in the nocebo group compared to control and was associated with enhanced low alpha (8–10 Hz) activity. However, changes in alpha activity were predicted by catastrophizing but not by pain intensity or unpleasantness, which suggest that low alpha power might reflect brain activity related to negative cognitive–affective responses to pain.

1. Introduction

Pain is a complex sensory and emotional experience that can vary widely between people, and even within an individual, depending on the context and meaning of the pain and the psychological state of the person (Bushnell et al., 2013). Affect and psychological processes such as expectancy and attention are important determinants of pain perception (Linton and Shaw, 2011). Expectation of a negative outcome can lead to pain worsening (nocebo hyperalgesia; (Colloca and Benedetti, 2007)), which might represent a point of vulnerability in the course of a disease and the response to a therapeutic intervention (Atlas et al., 2014; Benedetti et al., 2007; Bingel et al., 2011). A systematic review revealed that nocebo effects account for higher drop out rates and more adverse events in clinical trials in patients with chronic pain (Hauser et al., 2012), and occurs independently of the pharmacologic effects of treatment (Rutherford et al., 2014). Although identifying objective markers of nocebo could be helpful to predict nocebo-induced side effects and to design cognitive behavioral therapy and neurofeedback interventions for pain treatment, no quantification instruments of this phenomenon are known. So far, expectancy-based self-report assessments have been proposed as a prospective measure of placebo and nocebo responses in clinical interventions (Younger et al., 2012). Previous research has characterized the neural mechanisms underlying nocebo hyperalgesia using fMRI (Schmid et al., 2015; Schmid et al., 2013), but this method has limited clinical utility given its high costs. Thus, the present study sought to characterize quantitative EEG alterations related to pain facilitation by nocebo.

Although EEG markers for nocebo have not been previously investigated, research suggests that EEG alpha power is linked to clinical (Pinheiro et al., 2016) and experimental pain (Babiloni et al., 2014; Backonja et al., 1991; Chang et al., 2002; Egsgaard et al., 2009; Ferracuti et al., 1994; Nir et al., 2010, 2012), pain expectancy (Del Percio et al., 2006) and negative cognitive–affective responses to pain (Jensen et al., 2015). Anticipatory anxiety and negative expectation of pain worsening are determining factors of nocebo hyperalgesia (Aslaksen and Lyby, 2015; Benedetti et al., 2007; Elsenbruch et al., 2012; Ploghaus et al., 2001; Vogtle et al., 2013) and, as shown by neuroimaging studies, are associated with enhanced activity within the medial pain system (Kong et al., 2008; Ploghaus et al., 2001; Schmid et al., 2015). Because the medial pain system is an important source of alpha oscillation variability (Difrancesco et al., 2008; Goldman et al., 2002; Goncalves et al., 2006; Laufs et al., 2003) we expect that pain facilitation by nocebo will be associated with alterations in alpha EEG activity.

The current study aimed to characterize changes in EEG activity associated with nocebo hyperalgesia and to evaluate their relationship with cognitive-affective response to pain.

2. Methods

2.1. Participants

Participants were 52 healthy college students (24 males, 28 females, mean age 19.08 ± 1.15 years). Individuals reporting acute or chronic

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pain, physical or mental illness and those taking medication or recreational drugs on a regular basis were not included in the study.

2.2. Psychometric instruments

Before experiments, participants completed questionnaires to evaluate psychological factors that may interfere with pain perception.

The Center for Epidemiologic Studies Depression Scale (CES-D) was administered as a screening instrument to measure the current level of depression symptoms. This questionnaire consists of 20 self-report items scored on a 4-point Likert scale ranging from 0: rarely or none of the time to 3: most or all of the time. A cut off score 16 score is considered indicative of "significant" or "mild" depressive symptomatology (Radloff, 1977).

The State-Trait Anxiety Inventory (STAI) was used to evaluate anxiety symptoms. The STAI consists of two questionnaires of 20 items, each describing emotional conditions rated on a 4-point Likert scale. The range of scores for each subscale is 20–80, the higher score indicating greater anxiety. A score >40 has been suggested to be indicative of a clinically significant anxiety state (Knight et al., 1983).

The Pain Catastrophizing Scale (PCS) was administered to evaluate catastrophic thinking associated with pain. The PCS is a 13 item questionnaire and includes three subscales that evaluate rumination, magnification and helplessness (Sullivan et al., 1995). Participants are asked to recall thoughts and feelings related to past pain experiences and to indicate the degree to which they experienced each catastrophizing thought using a 0 (not at all) to 4 (all the time) Likert scale.

2.3. Experimental design and protocol

The study protocol was approved by the Texas A&M University Institutional Review Board and was carried out in accordance with the Declaration of Helsinki (World Medical A, 2013). All participants received information about the procedures and signed written consent to participate in the study. In exchange for participation, subjects received course credit.

Subjects participated in a one visit, 2.5-hour study. The study included a 2 (group: nocebo, control) × 3 (condition: rest, innocuous heat stimulation, noxious heat stimulation) × 2 (session: pre, post-intervention) design. Participants were randomly assigned to the nocebo or control group before any information about the study was given. Five-minute EEG recordings were acquired in (1) resting state, (2) innocuous heat stimulation and (3) noxious heat stimulation, before and after the cognitive manipulation.

2.4. Tonic heat stimulation

The experiments were conducted in a soundproof room with an ambient temperature 22–23 °C with participants seated in a comfortable reclining armchair. For heat stimulation protocols we used a computer controlled thermo-foil heating system (Pain and Sensory Evaluation system, Pathway, Medoc, Ramat Yishai, Israel). First, in order to familiarize participants with the testing procedure and the sensations induced by tonic heat, we conducted a training session that consisted of application of three short lasting (10 s) heat stimuli to the non-dominant volar forearm. Each stimulus was delivered from a 32.0 °C baseline at 1.0 °C/s increasing rate to distinct target temperatures (43, 45, 47 °C) to induce different intensities of heat- pain (Nir et al., 2012). After each stimulus, participants were asked to verbally report the intensity of pain using the 0 (no pain) to 100 (the most intense pain imaginable) numerical rating scale (NRS). The training session was followed by the determination of the individual intensity of the test stimulus ("pain-60", the temperature that induced a pain intensity scored 60 on the NRS). Pain-60 was employed to standardize the range of pain intensity for all tests and was determined before any information about cognitive manipulation was provided. In that order, 30 s tonic heat stimuli were applied at different intensities, starting with 45 °C and increasing/decreasing the temperature in a stepwise manner in 1 °C units until the perceived pain intensity was 60. The intensity of the test stimulus was confirmed by applying two heat stimuli at 1 °C above and below the temperature corresponding to "pain-60" (Granot et al., 2008; Nir et al., 2010). The subjects were excluded from the study if the individual "pain-60" was ≥47 °C due to Medoc-related safety protocol and also if their pain ratings were inconsistent across the trials (a difference of >10 points on the NRS for 2 identical heat stimuli, higher pain rating of a stimulus at a lower temperature or lower pain rating of a stimulus at a higher temperature).

2.5. EEG recording

The EEG data were recorded from 32 channels according to the 10–20 system using the BioSemi ActiveTwo system (band-pass filters: 0.4 and 100 Hz; sampling rate: 512 Hz with 24 bit resolution, average reference montage) and stored on disk for subsequent offline analysis. The electrodes were applied over an elastic cap with plastic electrode holders (BioSemi headcap) filled with electrode gel (Signa gel by Parker). The cap was available in 3 sizes and was chosen to best fit each individual. The electro-oculographic signals were recorded with two BioSemi FLAT Active electrodes. The Active Electrode has an output impedance of <1 Ω (compared to tens of kOhms with other systems), assuring that the signal in the cable is fully insensitive to interference (What are the advantages of Active electrodes, 2010). To ensure a good signal quality the electrode offset was kept below 40 mV.

During EEG acquisition participants were instructed to keep their eyes closed and stay relaxed but to remain awake. During innocuous and noxious heat stimulation, participants were asked to focus their attention on the heat-induced sensation, and the intensity of heat pain was verbally reported every 60 s using the earlier described NRS. Breaks of 15-minutes were maintained between two consecutive recordings.

2.6. Cognitive manipulation

In order to investigate the effects of nocebo on pain mechanisms and EEG activity, the study employed a deceptive information procedure. Subjects were told that the goal of the study was "to identify specific patterns of cerebral activity related with pain perception and pain modulation based on EEG recordings." For the cognitive manipulation an inert cream was applied for 15 min to the skin of all participants. Nocebo group participants were told that "the cream increases pain perception". In contrast, control group participants were told that "the cream is used to delimit the area of heat application between trials and has no effect on pain". At the end of study participants were asked to rate how strongly they believed that the applied cream was active or neutral (depending to which group they belonged) and the credibility of the manipulation was rated on a 0 (did not believe) to100 (totally believed) NRS (Vogtle et al., 2013). When the credibility of the manipulation was <100 we asked participants what other effects of the cream on pain perception they expected.

2.7. EEG data analysis

The continuous EEG recordings were imported to EEGLab, an interactive Matlab toolbox, for time domain analysis. The signal was segmented into 2 s long epochs, plotted and visually inspected for artifacts. We rejected EEG epochs contaminated with movement artifacts corresponding to the beginning of heat stimulation until the temperature reached the plateau, the epochs corresponding to verbal pain ratings conducted every 60 s after the stimulus' delivery, and also all epochs contaminated with blinks and eye movements. When at least one channel was contaminated with eye movements, blinking, muscle-twitches or speech artifacts the entire epoch was eliminated. The number of rejected epochs varied between conditions: 59.70 ± 15.48 (rest-pre); 58.60 ± 19.01 (innocuous stimulation-pre); 68.07 ± 18.66