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Pain perception and EEG dynamics: Does hypnotizability account for the efficacy of the suggestions of analgesia?

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HIGHLIGHTS

- Pain perception is modulated in highly hypnotizable Ss by suggestions of analgesia.
- Traits different from hypnotizability may be crucial in pain experience/EEG dynamics.
- The activity of the Behavioral Inhibition/Activation System (BIS/BAS) is one of them.
- BAS variability masks the role of hypnotizability in pain experience and EEG dynamics.
- BIS accounts for all the hypnotizability/stimulation/suggestions related EEG effects.

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ABSTRACT

We report novel findings concerning the role of hypnotizability, suggestions of analgesia and the activity of the Behavioral Inhibition/Activation System (BIS/BAS) in the modulation of the subjective experience of pain and of the associated EEG dynamics. The EEG of high (*highs*) and low hypnotizable participants (*lows*) who completed the BIS/BAS questionnaire was recorded during basal conditions, tonic nociceptive stimulation without (PAIN) and with suggestions for analgesia (AN). Participants scored the perceived pain intensity at the end of PAIN and AN. The EEG midline dynamics was characterized by indices indicating the signal predictability (Determinism) and complexity (Entropy) obtained through the Recurrence Quantification Analysis. The reduced pain intensity reported by *highs* during AN was partially accounted for by the activity of the Behavioral Activation System. The decreased midline cortical Determinism observed during nociceptive stimulation in both groups independently of suggestions remained significantly reduced only in *lows* after controlling for the activity of the Behavioral Activation System. Finally, controlling for the activity of the Behavioral Inhibition System abolished stimulation, suggestions and hypnotizability-related differences. Results indicate that the BIS/BAS activity may be more important than hypnotizability itself in pain modulation and in the associated EEG dynamics.

1. Introduction

Hypnotizability has been classically considered just as a cognitive trait enabling individuals to modify perception, memory and behavior according to suggestions' contents [1,2]. It is measured by scales and is receiving more and more interest in the physiological research [3] owing to the demonstration that also in the ordinary state of consciousness and in the absence of suggestions different levels of hypnotizability are associated with different cortical activity [4,5] and connectivity [6], sensori-motor integration [3,7,8] and cardiovascular control [9–11]. Such new view allows the consideration of hypnotizability much more than a cognitive trait and suggests its potential role in several processes and behaviors [3]. In the field of pain, it is widely known that hypnotic treatments are highly effective in chronic pain patients [12] and that hypnotizability is a good predictor of the efficacy of the suggestions for analgesia in both hypnotized and not hypnotized healthy individuals receiving nociceptive stimulation [13–18]. Nonetheless, it has been recently shown that also healthy participants with low hypnotizability scores (*lows*) can experience suggestions-induced analgesia during cold pressor test, although to a lower extent; indeed, they increase their pain tolerance, whereas individuals with high hypnotizability levels (*highs*) report reduced pain intensity and exhibit increases in both pain threshold and tolerance [18]. This suggests that other traits may interact with hypnotizability in the observed pain modulation [19]. In this

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respect, the possible role of the Behavioral Inhibition/Activation System (BIS/BAS), which mediates both emotion and cognition [20–23], has become of interest since it was shown that BIS/BAS buffers the *highs'* ability of nociceptive, but not of innocuous somesthetic imagery [24]. The Behavioral Inhibition System (BIS) is sensitive to novelty/punishment/non-reward, is associated with enhanced attention and arousal, is responsible for negative affect and harm avoidance and is involved in conflict monitoring and/or behavior inhibition [25] and in anxiety disorders [26–28]. It is based in septo-hippocampus networks, receives information from the prefrontal cortex and projects to the *locus coeruleus* and to the nuclei of the median *raphe*. The Behavioral Activation System (BAS), based in the septal area and in the lateral hypothalamus, is activated by appetitive stimuli, is sensitive to potential reward, mediates the emotion of anticipatory pleasure and is related to motivation to seek out positive experiences [20,23].

The spectral analysis of EEG recorded during tonic nociceptive stimulation has provided inconsistent results: the alpha power was found decreased over the temporal scalp contralateral to stimulation [29], larger ipsilaterally than contralaterally [30], increased over the posterior scalp during the cold pain conditions [29,31], decreased in the posterior part of the head only at the beginning of cold pressor test [32] and increased over the contralateral parietal locus [33]. In addition, alpha power obtained at the bilateral temporal scalp was found negatively correlated with tonic pain scores [34] and not correlated with them in other studies [35]. Inconsistent findings concern also the beta band, which was found increased bilaterally in frontal and posterior region [36], and increased unilaterally on temporal sites [31] and theta activity, which decreases at fronto-temporal sites according to a few authors [31] and increases in frontal areas together with delta activity [32] according to others [31].

With regard to pain modulation by hypnotic suggestions during tonic nociceptive stimulation, total and beta1 amplitudes have been found reduced [37] and the correlation between gamma activity and pain scores abolished [38], whereas suggestions administered after electrical stimulation reduced gamma activity at fronto-central midline sites [39].

Spectral analysis, however, may be not adequate to describe complex and often nonstationary systems like the brain [40], as it provides a picture of an EEG given time interval independently of its evolution in time; also the results obtained through recently introduced spectral indices taking time into consideration [41] are vitiated by the a-priori segmentation of the EEG in discrete bands. Methods analyzing the EEG dynamics are likely to better characterize the cortical activity [42,43]. Indeed, they have revealed sleep stages [44], conditions of consciousness/unconsciousness [45] and pre-ictal activity in epileptic subjects [46]. In particular, indices able to measure the EEG predictability and complexity (see Supplementary Electronic Material) discriminated *highs* and *lows* during simple relaxation [5] and, in combination with other methodologies, characterized as hypnotized and not hypnotized participants [47,48]. Thus, these indices may be particularly useful to analyze the EEG cortical dynamics associated with the subjective experience of pain and of its modulation by suggestions of analgesia in *highs* and *lows*.

The aim of the present study was to characterize the pain-related brain dynamics sustaining the *highs'* and *lows'* subjective experience of pain and to study the effects of the interaction of hypnotizability with the activity of the Behavioral Inhibition/Activation System in both the subjective experience and cortical dynamics.

2. Methods

The study protocol followed the rules of the Declaration of Helsinki and was approved by the Ethics Committee of Pisa University.

2.1. Subjects

After written informed consent, the *Italian* version (Organizzazioni Speciali, Firenze) of the Stanford Hypnotic Susceptibility Scale (SHSS), form A [49] was administered to 75 healthy males who volunteered for hypnotic assessment. Among them, all the participants scoring high at SHSS (*highs*, N = 8; SHSS score (mean ± SD): 9.7 ± 1.1) and 10 individuals with low hypnotizability (*lows*, SHSS score: 1.5 ± 1.4) randomly sorted among all *lows* (N = 31) were enrolled in the study (age, mean ± SD: 22 ± 1.8 years). In fact, we decided to include a number of *lows* approximately similar to the number of *highs* found in the sample and not to study medium hypnotizable participants (N = 36) who are more heterogeneous than *highs* and *lows*, as they may respond to different items of susceptibility scales and obtain the same total hypnotizability score. Neurological, psychiatric and systemic diseases were ruled out by detailed clinical history. On the day of the hypnotic assessment, participants completed the BIS/BAS questionnaire [50] which measures the activity of the Behavioral Inhibition/Activation System. In order to minimize the possible effects of the expectancy of hypnosis, subjects were informed that no hypnotic induction would be performed in the experimental session, which was scheduled 4–6 weeks after hypnotic assessment.

2.2. Experimental procedure

Sessions were carried out between 2.00 and 4.00 p.m., at least 4 h after the latest light meal and 6 h after the latest caffeine containing beverages, in a semi-darkened, sound-attenuated and temperature-controlled room (20–25 °C). Four eyes closed conditions were included: baseline (B1, 5 min), corresponding to the latest 5 min of a longer relaxation interval which was the object of another study [5], tonic nociceptive stimulation (PAIN, 2 min), baseline (B2, 5 min) and tonic nociceptive stimulation with suggestions for analgesia (AN, 2 min). The side of PAIN and AN stimulation was randomized among subjects. The B1-PAIN and B2-AN sequences were pseudo-randomized among *highs* and *lows*.

For both PAIN and AN, nociceptive stimulation consisted of a 2 min pressure applied to the second costo-chondral junction (the *joint* between the second ribs and costal cartilage in the front of the rib cage) through a deep pressure algometer (Wagner Instruments, Greenwich CT) providing the force exerted on the application surface (1 cm^2). Stimulation was set in each subject at the beginning of the session (before the entire long relaxation interval) by progressively increasing pressure at a rate of approximately 1 kg/s. The pressure increase was stopped when the subjects declared to feel "moderate" pain (5–6 on a scale ranging from 0 to 10) on both the right and left sides. The intensity of stimulation needed to elicit this moderate pain was independent of hypnotizability (*highs*, 3.0 ± 0.10; *lows*, 3.04 ± 0.13) and body side (right: 3.02 ± 0.11; left: 3.05 ± 0.10).

The script of the suggestions for analgesia, which was read to all participants by the same experimenter (ELS), described the absence of any pain due to interruption of the information flow (from *Italian*: "… *your nerves do not transmit any pain sensation to your brain* …"), the impossibility to feel/remember pain ("… *you cannot feel and even remember any pain* …"), and to attribute any pain to themselves ("… *pain does not belong to you* …"). Instructions for relaxation were also included in the script.

2.3. Signal acquisition and preprocessing

Standard electroencephalographic recordings (32-channels for EEG, 8-ch for auxiliary signals; sampling rate: 1000 Hz; band-pass filter: 0.1–100 Hz) were performed according to the International 10–20 System by Ag/AgCl electrodes embedded in an elastic cap (Quick-Caps from Compumedics/Neuroscan). Scalp EEG signals grounded at FPz were referenced to the FCz potential; then, the records were re-referenced off-