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# Neuroelectric evidences of top-down hypnotic modulation associated with somatosensory processing of sensory and limbic regions

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ABSTRACT

A large literature indicated hypnosis as a useful tool to reduce pain perception, especially in high susceptible individuals. However, due to different methodological aspects, it was still not clear whether hypnosis modulates the early sensory processing of the stimuli or if it affects only the later stages of affective processing. In the present study, we measured the EEG activity of subjects with a medium level of hypnotizability while receiving electrical non-painful stimuli on the median nerve in the conditions of awake and hypnosis with suggestions of hypoesthesia. Subjective reports indicated that hypnosis reduced both the sensory and the affective perception of the stimuli. ERP data revealed that hypnosis reduced the activity of both the early (N20) and the late (P100, P150, P250) SEP components. Neuroelectric source imaging further confirmed the top-down hypnotic modulation of a network of brain areas including the SI (N20), SII (P100), right anterior insula (P150) and cingulate cortex (P150/P250). The present study provides neurophysiological evidence to the hypnotic regulation of somatosensory inputs outside of pain, that is since the earliest stage of thalamocortical processing. Also, because present subjects were selected regardless of the level of hypnotizability, inferences from the present study are more generalizable than investigations restricted to high-hypnotizable individuals.

## 1. Introduction

The susceptibility to hypnosis was defined as a stable personality trait (Piccione et al., 1989), and both trait- and state-dependent activities of different brain regions have been reported as a biological marker of hypnotizability (for a review see Vanhaudenhuyse et al., 2014). Furthermore, several studies indicated hypnosis as a useful tool to reduce painful sensations (for reviews see Chaves and Dworkin, 1997; Jensen and Patterson, 2006), and some hospitals adopt hypnosedation as a routine procedure in surgery (e.g. Vanhaudenhuyse et al., 2009). In fact, pain experience depends on the interaction between sensory-discriminative and affective-motivational components (Towell and Boyd, 1993; Price et al., 1999; Treede et al., 1999), and the subjective perception may reflect the contribution of both: as a consequence, the individual reports do not answer the original question, and brain activity measures are needed. Furthermore, somatosensory and pain processing share apartly overlapping neural network composed by primary and secondary somatosensory area, anterior cingulate cortex and insula (Schnitzler and Ploner, 2000). Here, we excluded contribution of pain experience in sensory modulation and then focused on neural mechanisms underlying the hypnotic modulation of somatosensory inputs. Thus, we used non painful stimuli in order to test whether hypnosis affects the early processing of the sensory cortices or if it modulates the later stages of information processing, such as the affective integration by the frontal and parietal associative areas.

Electroencephalogram (EEG), and especially the event-related potentials (ERPs), represent an optimal technique to catch the fast succession of brain events associated with the administration of sensory stimuli. Previous studies measured the modulation of the somatosensory-evoked potentials (SEPs) as an effect of hypnotic state (e.g., Spiegel et al., 1989) and hypnotizability *per se* (i.e., outside of hypnosis; Del Percio et al., 2013). Even if an EEG study on gamma oscillations suggested sensory alteration by hypnosis (De Pascalis et al., 2004), most investigations indicated the cognitive and affective integration of the somatosensory stimulus as the locus of the hypnotic effect, as reflected by modulations of the late N140, P200 and P300 components (Spiegel et al., 1989; De

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Pascalis et al., 1999, 2001; 2008; Ray et al., 2002; Del Percio et al., 2013). However, it should be noted that SEPs evidence is not always consistent with neuroimaging findings that reported hypnotic modulations also in sensory-related structures such as the brainstem, thalamus, and primary somatosensory (SI) cortex (Rainville et al., 1999, 2002; Faymonville et al., 2000, 2003; Vanhaudenhuyse et al., 2009). The reasons for these contrasting findings could be twofold. First, because of the low temporal resolution of the neuroimaging techniques, these studies detected differences in the late affective processing of the sensory areas, but the effects were erroneously attributed to the earliest processing of the sensory input. As a second hypothesis, because of the different experimental conditions adopted by SEP studies (e.g., five conditions in De Pascalis et al., 2008), the low number of trials (often less than 100) did not allow to extract the early SEPs, and investigations were limited to the late components. Indeed, note that at least 500 artifact-free trials are needed for the early SEPs identification (American Clinical Neurophysiology Society (ACNS), 2006).

Because of the methodological limitations reported above, and the need to clarify whether hypnosis can affect somatosensory processing beyond painful sensations, in the present study we investigated the effects of hypnosis on the early and late components of SEPs. To this aim, electrical non-painful stimulation was administered on the median nerve in the conditions of awake and hypnosis with suggestions of hypoesthesia; further, a high number of trials was provided (1200 stimuli per condition). Finally, differently from previous studies in this field, we did not select subjects based on their hypnotic responsiveness; at the opposite, we included all subjects in the study regardless of the level of hypnotizability that was measured through a standardized scale. In fact, most studies on hypnosis used to compare individuals with high and low levels of hypnotizability ("Highs" vs "Lows"), typically leading to greater experimental effects for the former group. However, since Highs and Lows correspond to the minority of the population, these findings might be scarcely generalizable to the majority of the "Medium" (see also Jensen et al., 2017 on this point). For this reason, we adopted a correlational approach instead of a categorical one as it prevents any possible bias associated with the unique characteristics of the high susceptible individuals. Finally, it is noteworthy that recent guidelines on hypnosis research raised the importance of the hypnotic induction techniques as well (Jensen et al., 2017). In fact, even if most scientists consider the induction as an essential part of hypnosis, more research is needed to understand if different techniques (e.g., remaining alert vs. muscle relaxation) may account for different effects. For this purpose, we describe in detail the hypnotic induction and suggestion with the aim to help future research on this point.

## 2. Materials and methods

### 2.1. Participants

Twenty-five participants (12 males; mean age = 22.2 years, SD = 1.4) volunteered to participate in the experiment: they were recruited from the student population at the University of Rome "Foro Italico" and received one extra credit on the psychology exam for their participation in the experiment. Participants had a normal or corrected-to-normal vision, no previous experience with hypnosis and no history of neurological or psychiatric disorders; all participants were right-handed (Edinburgh handedness inventory; Oldfield, 1971).

Participants gave their written informed consent for their participation in the study. The procedures were approved by the local ethics committee and were in accordance with the ethical standards of the 1964 Declaration of Helsinki.

### 2.2. Procedure and stimuli

For each subject, participation in the experiment consisted of two sessions at a distance of at least one week: the first was to assess the individual level of hypnotic susceptibility, the second to record the EEG activity in the awake and hypnosis condition.

The hypnotic susceptibility was assessed through the administration of the Italian translation of the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS: A) within three group sub-sessions. During each sub-session, the 12 standard suggestions from HGSHS: A were administered orally by an experienced hypnotherapist (no audio recording was used). At the end of each session, the participants were given a response booklet and asked to report their experience filling in an "objective" score form and a "subjective" score form. Only the "objective" score form was considered for the determination of the participants' individual score, following the standard procedure described by Shor and Orne (1962). For each of the first 11 items, a score of 1 was attributed if the subject had reported having experienced the suggested response; a score of 0 was attributed in the opposite case. For the 12th item, regarding posthypnotic amnesia, a score of 1 was attributed if less than 4 items had been reported in the response booklet before amnesia was lifted; otherwise, a score of 0 was attributed.

In the second session, the EEG of each participant was recorder while somatosensory stimuli were administered on the left median nerve. The EEG session consisted of two conditions, provided in a counterbalanced order across subjects: awake relaxed and hypnosis. In the awake relaxed (from now on, awake) condition, participants were asked to close their eyes and relax their mind during all the SEP recording (about 18 min). In the hypnotic condition, a suggestion of hypoesthesia was administered after the hypnotic state was induced. Depending on the individual resting time, a few minutes separated the first and the second condition (i.e., hypnosis or awake first depending on the order). The hypnotic induction procedure was structured as follows: the subject was invited to observe the tip of the operator's index finger. This target was made to move slowly following a trajectory in the shape of 8, while suggestions of heaviness of the eyelids were imparted. The operator continued with the movement of the target finger and with suggestions until the eyes of the subject were closed. At this point, the operator gave suggestions to obtain the progressive relaxation of the body. The subject was asked to focus attention on the respiratory act, while the operator suggested a sense of heaviness and softness directed to the different bodily segments, in the cranio-caudal direction. After the muscular relaxation condition was obtained and deepened, the operator verified whether participants were hypnotized by observing the presence of signals, such as easing of facial tension, dropping of the lower jaw accompanied by a slight opening of the mouth, and slowing of the breathing rate (Casiglia et al., 2006). After the hypnotic state was correctly induced, the operator started to administrate the suggestions of hypoesthesia: in order to avoid inter-individual differences, a standard script was adopted (see supplementary material). After, the experimenter started to administrate the somatosensory stimuli, that did not change in intensity across conditions (see next section for details on the electrical stimulation). No further suggestions of hypoesthesia were given after the stimulation started: the hypnotist remained silent until the end of the stimulation, when the de-induction procedure was administered (i.e., a slow count from 1 to 3 before opening the eyes). At the end of each condition, participants were asked to rate the intensity and unpleasantness of the stimulation on two visual analog scales (VAS, from 0 to 10 with 10 corresponding to the maximum level). For the measurement of the sensory VAS (s-VAS), participants were asked to "indicate how clearly the stimuli were perceived"; for the measurement of the affective VAS (a-VAS), participants were asked to "indicate the level of unpleasant feeling associated with stimuli".

### 2.3. SEP recording

Somatosensory stimuli consisted of 0.5 ms non-noxious square waves generated by a constant current stimulator (STM 140; HTL, Udine, Italy) through surface skin electrodes placed over the median nerve of the non-dominant upper limb at the wrist, with the cathode proximal to the

anode. Stimulation intensity was determined for each subject by delivering a series of stimuli at an increasing intensity from 2 mA in steps of 1 mA until reaching the motor threshold, identified by the slight thumb twitching. The inter-stimulus-interval (ISI) was between 600 and 1200 ms (mean 900 ms) with random order. Each condition consisted of three 6-min runs of 400 stimuli each, for a total of 1200 stimuli per condition. Participants were tested in a sound attenuated, dimly lit room: they were comfortably seated with the left arm comfortably resting on a pillow. The EEG signal was recorded using two BrainAmp™ amplifiers connected with 64 ActiCap™ active electrodes (BrainProducts GmbH, Munich, Germany) mounted according to the 10-10 International system. The ground electrode was positioned on the left forearm, and all electrodes were referenced to the left earlobe (see Fig. 1 for the experimental set-up).

Electrode impedances were kept below 5 KΩ, and all signals were low-pass filtered (1000 Hz), digitized (rate of 1000 Hz) and stored for off-line averaging. Artifact rejection was performed to discard epochs contaminated by signals exceeding the amplitude threshold of ±60 μV. Two subjects have been removed from the dataset due to the high number of artifacts, mostly due to the head drops during hypnosis. Accordingly, data of twenty-three subjects (11 males; mean age = 22.1 years, SD = 1.5) were considered for EEG analysis. On average, about 15% of the trials in each condition were rejected due to the presence of artifacts, and on average 1020 artifact-free trials were collected for each condition.

For analysis of the early and late SEPs, the signal was segmented in different ways. For the early SEPs, the EEG was band-pass filtered between 3 and 200 Hz, and segmented for each electrical stimulus giving epochs of 120 ms (−20 to 100 ms); the baseline was calculated from 20 ms to 1 ms before the electrical stimulus to avoid any stimulus artifact. For the late SEPs, the EEG was low pass filtered (Butterworth cut-off frequency 70 Hz, slope 24 dB/octave) and segmented giving epochs of 700 ms (−100 to 600) with the first 100 ms serving as the baseline. The segmented trials were finally averaged, and the grand averages of SEPs recorded in the awake and hypnosis condition were obtained.

### 2.4. Data analysis

Based on grand-average scalp topography and indications from previous investigations (e.g., Bufalari et al., 2007), latency and amplitude of SEPs were calculated on the individual peaks as follows: P15 on Fz, N20 on P8, P25 on C4, N30 on Fz, P45 and N60 (the latter as the peak-to-peak distance) on CP4, P100 on P2, P150 on FCz, P250 on C2. The subjective ratings and the SEP values were compared between awake and hypnosis condition with t-tests for dependent samples and corrected for multiple comparisons using Bonferroni correction (Brown et al., 1991) by multiplying the observed p values by the number of considered components (i.e., 9 between early and late SEPs). Effect sizes (Cohen's *d*; Cohen, 1988) were calculated correcting for the dependence between means for within-subjects effects. According to Cohen (1988), effect sizes were considered small ($d < 0.20$), moderate ($0.20 \leq d \leq 0.80$), or large ($d > 0.80$) In addition to the *t*-test, we also calculated the Bayes Factor (BF) for each comparison to better assess the statistical power of null hypothesis. This calculation assumed an effect size of r = 0.707 and proving a scaled-information BF value. BF below 10 support the null hypothesis (Rouder et al., 2009). Further, the SEP values, the susceptibility scores and the subjective ratings (both global and differential VAS) were correlated with each other (Pearson's *r*). The overall alpha level was fixed at 0.05.

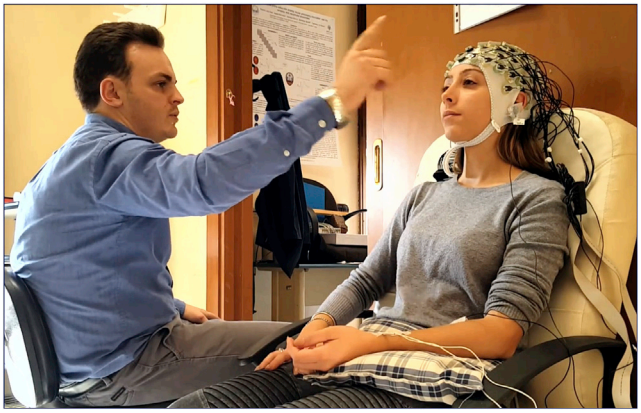

**Fig. 1.** Experimental set-up: the eye-fixation stage of the hypnotic induction.

### 2.5. Neuroelectric source imaging

The neural source of the SEPs was estimated using the sLORETA software, which is a functional imaging method based on electrophysiological and neuroanatomical constraints (Pascual-Marqui, 2002), able to localize both superficial and deep brain structures (Pizzagalli et al., 2004; Zumsteg et al., 2006) using EEG data. The source analysis was performed in the time frames where the ERPs were significantly modulated (i.e., defined as the group mean of the individually-calculated latency for each component). After that, current source density (CSD) waveforms of representative regions of interest (ROIs) were obtained, yielding high-resolution temporal curves.

## 3. Results

### 3.1. HGSHS and subjective reports

The average level of susceptibilityon the HGSHS in the sample was 7.3 (SD = 1.8), indicating a medium level of responsiveness to hypnosis.

As shown in Fig. 2, the perceived intensity of the somatosensory stimulation (s-VAS) was reduced from the awake (mean = 8.8, SD = 1.2) to hypnosis condition (mean = 6.3, SD = 2.6; t = 5.5, p < 0.0001), and the affective rating (a-VAS) also decreased from the awake (mean = 3.9, SD = 2.5) to hypnosis condition (mean = 2.8, SD = 2.3; t = 2.4, p < 0.05). In other terms, the reduction rate from awake to hypnosis was 28.4% and 28.2% for the sensory and affective perception respectively. No significant correlations emerged between the HGSHS level and the VAS ratings (all ps > 0.05, BFs<10).

### 3.2. Electrophysiological data

Fig. 3a shows the grand average of the early SEPs in the two conditions. At Fz site, the P16 and the N30 were clearly detectable but not modulated between conditions. The other SEP components presented right central-parietal distributions contralateral to the stimulated median nerve. Specifically, the N20 was larger in the awake than hypnosis condition, while the P45 presented an opposite trend and was followed by the N60 on the same site. The P25 emerged on the right central area of the scalp. Scalp topography of the N20 component is represented in Fig. 3b showing the typical tangential distribution centered over the contralateral hemisphere and similar between conditions.

Statistical analysis on the latency of the early SEPs did not report significant differences between conditions (ps > 0.05, BFs<9.32). Table 1 reports statistical analysis on the amplitude of the early SEPs: as can be seen, a significant difference emerged for the N20 component, that was reduced in hypnosis by 42%.

Fig. 4 shows the grand average of the late SEPs in the two conditions. The main detectable components were the P100, the P150 and the P250 on the parietal, frontal-central and central areas respectively. The activity of all these components decreased in hypnosis, and their topography was tangential for the P100 and P150, radial for the P250, as shown in the scalp maps of Fig. 5. The visual inspection of the surface topographies suggests similar ERPs scalp distribution between conditions.

Statistical analysis confirmed that all the late SEPs were modulated

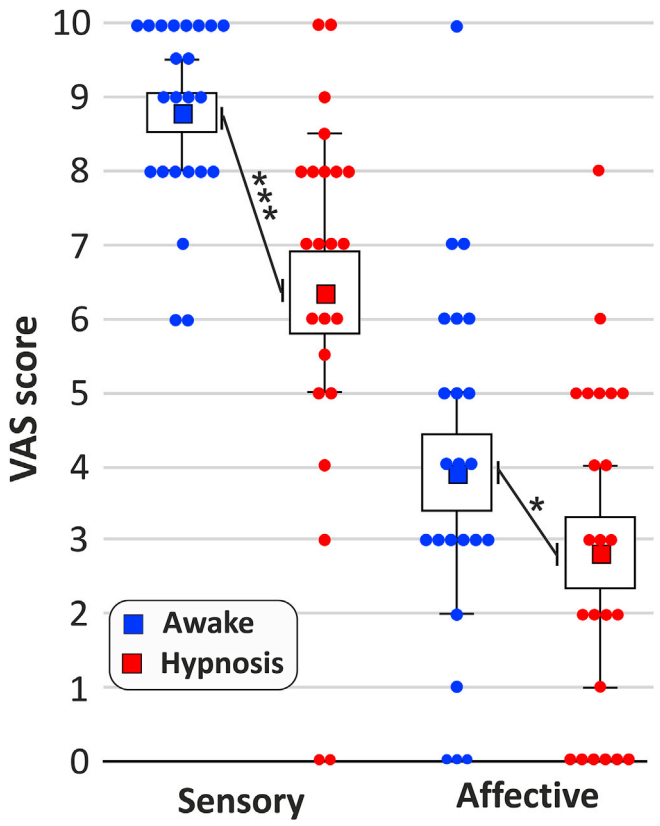


**Fig. 2.** Box plots (small central boxes, mean; boxes, ±SE; whiskers, non-outlier range) of the visual analog scales (VAS) for the sensory and affective components of the somatosensory perception in the two conditions. Individual data are plotted on top of the box plots *p < 0.05, ***p < 0.001.

between conditions: specifically, the P100 was larger ($t = 4.5$, $p < 0.001$, $d = 0.91$, BF = 226) in awake (2.0 μV, SD = 1.2) than hypnosis (1.3 μV, SD = 1.0); the P150 was larger ($t = 4.6$, $p < 0.001$, $d = 0.99$, BF = 279) in awake (2.7 μV, SD = 1.1) than hypnosis (2.1 μV, SD = 1.1), and the P250 was larger ($t = 3.3$, $p < 0.05$, $d = 0.79$, BF = 18) in awake (2.2 μV, SD = 1.0) than hypnosis condition (1.7 μV, SD = 0.9). At the opposite, no difference of latency emerged between SEP components for the two conditions (all ps > 0.05). Correlational analyses indicated that neither amplitude nor latency of all the considered components (i.e., early and late) correlated with the HGSHS and the global VASs. In order to control for a more suited effect-specific test, we also calculated the differential values (i.e., awake minus hypnosis) for VAS domains and ERP data of the modulated components. Correlational results (Pearson's r) are reported in Table 2.

Correlational analysis revealed significant associations between the differential scores of the two domains of the subjective ratings (VAS), indicating that hypnotic reduction in sensory perception was paralleled by a reduction in the perceived unpleasantness of the electrical stimulation. Further, the differential score of the affective VAS significantly correlated with modulation of the P250, suggesting a role for this component in the affective component of the somatosensory processing (see below for a discussion on this point).

The neuroelectric source imaging was obtained for the significant SEP components, and the main generators are listed in Table 3; note that all the reported ROIs were predominantly (or exclusively) active in the right hemisphere, contralateral to the stimulated nerve.

As can be seen, and accordingly to the literature (e.g., Allison et al., 1992), the source of the early SEP (N20) was localized mainly in the primary somatosensory area (SI), while the P100 was also generated by the activity of the secondary somatosensory area (SII). On the other hand, less was known on the source of the P150 and P250 components, that present analysis localized in both common and specific areas. Common areas included the middle frontal gyrus and the cingulate cortex, that was anterior for the P150 and more posterior for the P250. Specific areas of activation for the P150 included the paracentral lobule and the anterior insula (aIns). Since, to the best of our knowledge, the aIns activity was never described through SEPs, we extracted the CSD waveforms corresponding to the insular ROI (voxels centered at x = ±35 y = −10 z = 20 MNI coordinates) for a further investigation. Fig. 6a shows the CSD waveforms of the bilateral aIns in the two conditions, and Fig. 6b the activation of the corresponding voxels1 at 150 ms, that is the time when the right insular activity (and the corresponding P150 on the scalp) was reduced in hypnosis.

As can be seen in the Figure, the profile of activation of the anterior insula was different across hemispheres. In fact, the intensity of activity from the left insula was always smaller than right. Moreover, a difference between conditions emerged at 150 ms, when the mean activity of the right insula was of 5.3 nA/m$^2$ and 4.0 nA/m$^2$ in the awake and hypnosis condition, respectively. In other terms, at 150 ms after the stimulus the hypnotic hypoesthesia reduced by 32.5% the intensity of the somatosensory processing in the right insula.

### 3.3. Descriptive statistics in subgroups of high-, medium- and low-hypnotizable subjects

The present study was conceived with a correlational approach, that is selecting participants regardless of the level of hypnotizability. However, as most literature used to compare high- and low-hypnotizable subjects, it may be useful to classify also participants of the present study in different subgroups of susceptibility with the only aim to observe their mean data. For this purpose, we referred to the HGSHS score to select the samples of High-hypnotizable (HGSHS from 9 to 12, mean = 9.7; N = 7), Medium-hypnotizable (HGSHS from 6 to 8, mean = 7.2; N = 10) and Low-hypnotizable (HGSHS from 0 to 5, mean = 4.8; N = 6). However, due to the scarce presence of very low-hypnotizable, criteria for defining Lows were a bit different from those adopted in the literature (i.e., Low-hypnotizable are usually defined by an HGSHS score below 4). Data of the main SEPs are reported in Table 4 for each subgroup: both absolute and differential values (i.e., awake minus hypnosis) are considered. Because of the small size of the samples, ERPs are not suitable for statistical analysis and no further comparisons were performed on these data.

If considering the hypnotic reduction effect (i.e., the differential values), Table 4 seems to suggest that the larger difference between groups emerged in the N20 component, for which amplitude of Highs, Medium and Lows decreased respectively by 1.1, 0.3 and 0.3 μV. On the other hand, amplitude modulation of the P100, P150 and P250 components was similar across subgroups. As regards the subjective reports, the sensory rating decreased in hypnosis by 2, 2.6 and 2.6 points in the samples of High, Medium and Lows respectively; the affective rating decreased in hypnosis by 0.7, 1.4 and 1 points in the same samples. In other words, subjective ratings would suggest that sensory and affective perception of Medium and Lows decreased more than Highs as an effect of hypnosis. However, as these samples are small and not very representative (e.g, the mean HGSHS of Lows was higher than 4), theoretical inferences cannot be drawn from these data.

## 4. Discussion

To the best of our knowledge, this is the first study that measured early and late ERPs to investigate hypnosis effects during somatosensory brain processing. Further, this study was not carried out on individuals with special responsivity to hypnosis. In fact, the assessment of hypnotizability level showed that present subjects are mostly in the medium range of responsiveness so that inferences from the present study are more generalizable than investigations restricted to high-susceptible individuals.

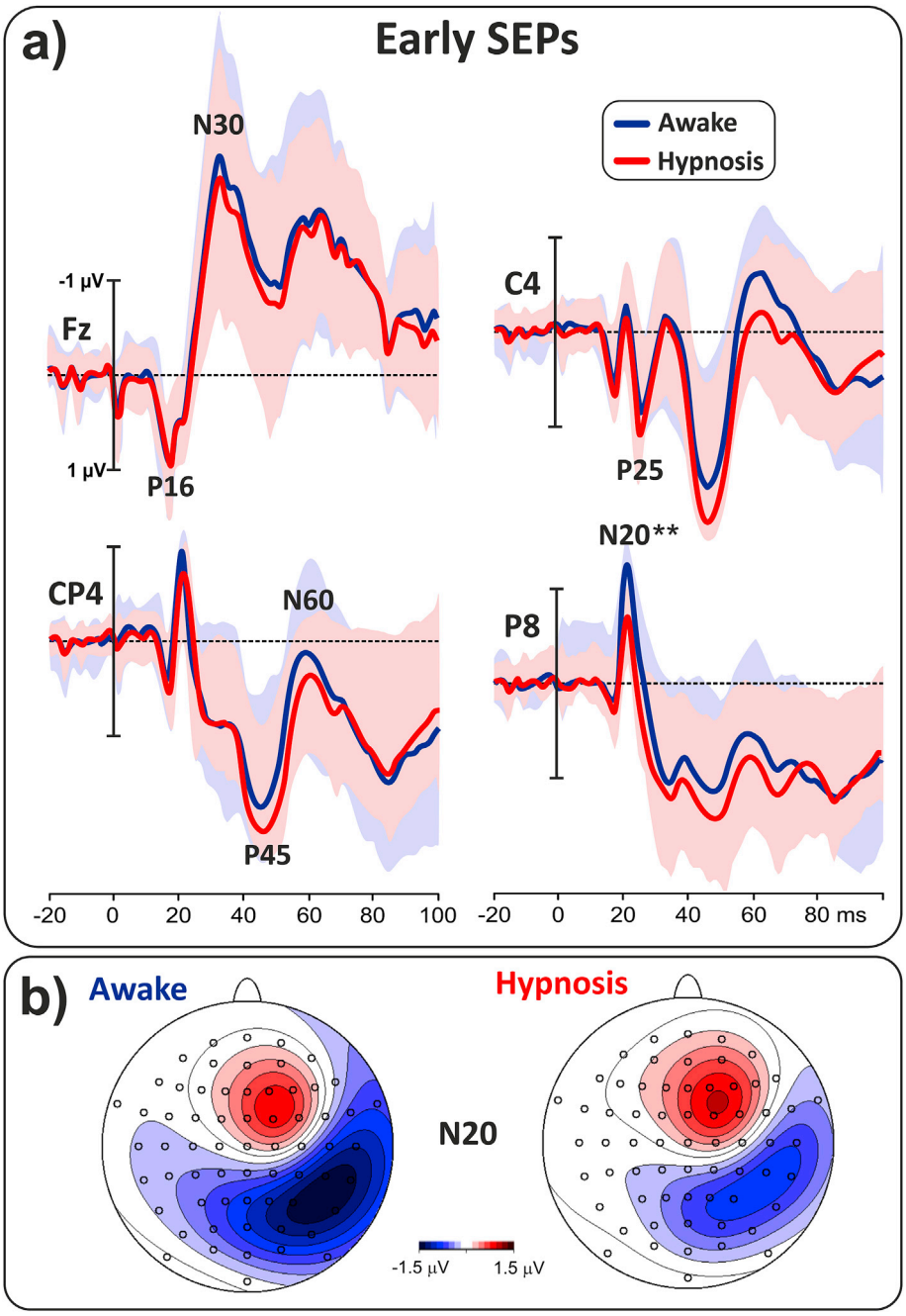


**Fig. 3.** a) Grand-average waveforms of the early SEPs in the awake and hypnosis condition. Standard deviations are reported above and below the mean as a shaded area. **p = 0.01. b) Topographic maps of the N20 component in the two conditions.

### 4.1. Subjective reports

Analysis of the visual analog scales revealed a reduction of 28.4% and 28.2% for the sensory and affective perception of somatosensory stimuli from awake to hypnosis condition. However, as the main goal was to investigate hypnosis effects on the sensory perceived intensity, we adopted non-painful electrical stimulation: as a consequence, the perceived unpleasantness was rather low in the awake condition (mean value of 3.9 in a 0–10 scale), and it is possible to suppose even a greater reduction when adopting hypnosis with painful stimuli (see e.g., De Pascalis et al., 2008). Interestingly, the subjective ratings on the sensory and affective VAS did not correlate with the level of hypnotizability, indicating that the modulation of sensory perception by hypnotic hypoesthesia was not mediated by the level of susceptibility to hypnosis.

### 4.2. Early SEP components

Analysis of the early SEPs indicated a significant decrease of the N20 amplitude as an effect of hypnosis. Source analysis of the present study indicated the postcentral gyrus as the main generator of the N20, according to studies that described it as the ERP from the SI area, in the posterior wall of the central fissure (e.g. Mauguiere et al., 1999). More specifically, a transcortical recording obtained during neurosurgery identified the source of the N20 in the deep of the contralateral area 3b of the SI (Allison et al., 1989). It is noteworthy that area 3b receives inputs from the pulvinar nuclei of the thalamus and is activated only by somatosensory stimuli. These evidence suggest that hypnosis affected the somatosensory activity since the first stages of cerebral processing, that is by reducing the signal intensity at the level of the thalamocortical

**Table 1**
Statistical comparison between the amplitude of the early SEPs in the awake and hypnosis condition. p values are corrected for multiple comparisons. Effect sizes (Cohen's *d*) and Bayes factor (BF) were reported.

| Component | Site | Condition | Amplitude (SD) | t (p) | *d* | BF |
|---|---|---|---|---|---|---|
| P16 | Fz | Awake | 1.0 (0.6) | 0.1 (ns) | 0.0 | 3.59 |
| | | Hypnosis | 1.0 (0.6) | | | |
| N20 | P8 | Awake | −1.4 (0.6) | **3.5 (0.01)** | **0.79** | **27.83** |
| | | Hypnosis | −0.8 (0.5) | | | |
| P25 | C4 | Awake | 1.2 (0.7) | −1.6 (ns) | 0.2 | 1.12 |
| | | Hypnosis | 1.4 (1.0) | | | |
| N30 | Fz | Awake | −2.7 (1.3) | −1.4 (ns) | 0.3 | 1.46 |
| | | Hypnosis | −2.4 (1.3) | | | |
| P45 | CP4 | Awake | 2.1 (1.1) | −2.4 (ns) | 0.5 | 3.22 |
| | | Hypnosis | 2.6 (0.9) | | | |
| N60 | CP4 | Awake | −0.3 (1.0) | −2.5 (ns) | 0.5 | 3.87 |
| | | Hypnosis | 0.2 (1.0) | | | |

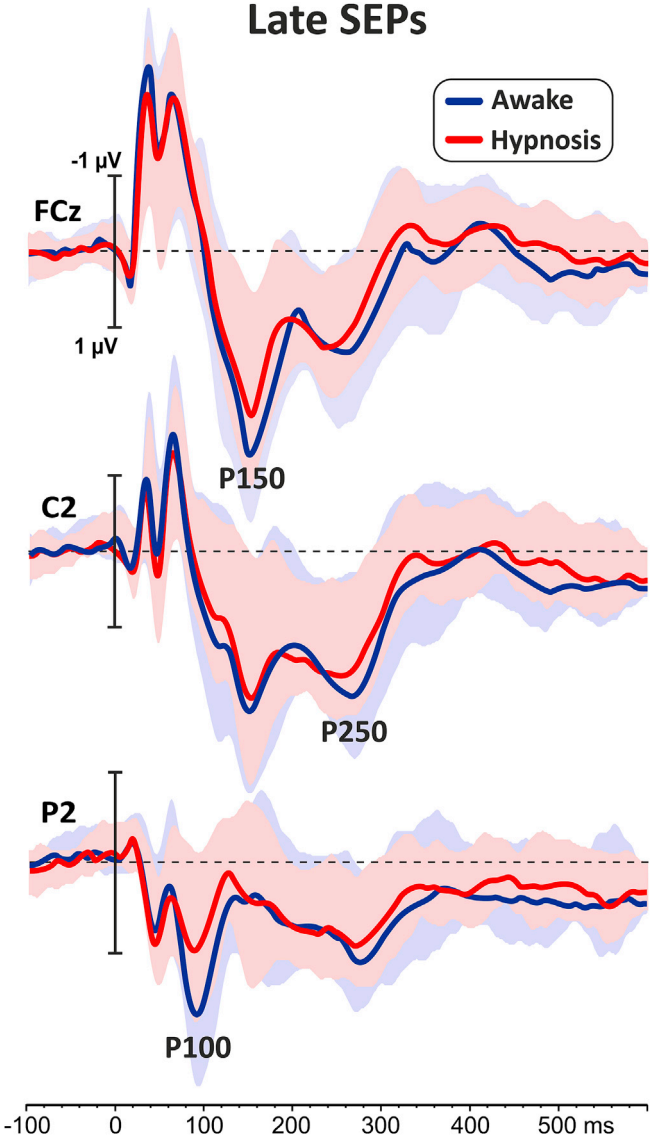


**Fig. 4.** Grand-average waveforms of the late SEPs in the awake and hypnosis condition. Standard deviations are reported above and below the mean as a shaded area.

radiations. This result was never described before in an ERP study but is consistent with neuroimaging findings on high-susceptible individuals (e.g., Vanhaudenhuyse et al., 2009). It is interesting to note that

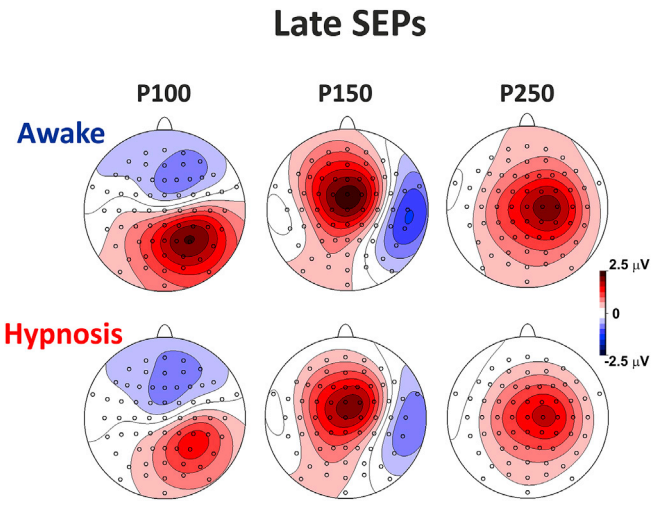


**Fig. 5.** Topographic maps of the P100, P150 and P250 components in the two conditions.

**Table 2**
Correlational analyses between susceptibility score (HGSHS), differential values (Diff.) of subjective (VAS) and neurophysiological (SEP) data. r (p) values are reported.

| | Diff. VASs | Diff. VASa | Diff. N20 | Diff. P100 | Diff. P150 | Diff. P250 |
|---|---|---|---|---|---|---|
| Diff. VASs | | **.57 (< 0.01)** | .16 (ns) | .25 (ns) | .04 (ns) | .28 (ns) |
| Diff. VASa | **.57 (< 0.01)** | | .19 (ns) | .16 (ns) | .16 (ns) | **.57 (< 0.01)** |
| HGSHS | .00 (ns) | .07 (ns) | -.31 (ns) | -.02 (ns) | -.3 (ns) | -.03 (ns) |

**Table 3**
ROIs of maximum activation in the mean latency of the selected SEPs (L = left, R = right).

| SEP component | Anatomical region | Brodmann area | Hemisphere |
|---|---|---|---|
| N20 | Precentral gyrus | 4/6 | R |
| | Postcentral gyrus | 3 | R |
| P100 | Postcentral gyrus | 2/3/4 | L/R |
| | Superior parietal lobule | 5 | L/R |
| P150 | Medial frontal gyrus | 6 | L/R |
| | Insula | 13 | R |
| | Anterior Cingulate gyrus | 24 | L/R |
| | Paracentral lobule | 31 | L/R |
| P250 | Cingulate gyrus | 23/24 | L/R |
| | Medial frontal gyrus | 6 | L/R |

decreases of the N20 were only observed as an effect of nitrous oxide during anesthesia (Sebel et al., 1984), while results from cathodal transcranial electrical stimulation of the sensorimotor cortex are contrasting (Matsunaga et al., 2004; Dieckhöfer et al., 2006).

### 4.3. Late SEP components

In general, somatosensory potentials evoked 100 ms after the stimulus reflect activity from the SII, posterior parietal and frontal cortices (Allison et al., 1989, 1991; 1992; Forss et al., 1996), and have been associated to activity of the frontoparietal networks involved in cognitive and attentional integration of somatosensory signals (Desmedt and Tomberg, 1989; Schubert et al., 2006, 2008). The present study revealed a decrease of the P100, P150 and P250 components as an effect of hypnotic suggestions of hypoesthesia. Findings on the P100 are consistent with results from Spiegel et al. (1989) and might reflect a reduction of the somatosensory conscious perception (Schubert et al., 2006).

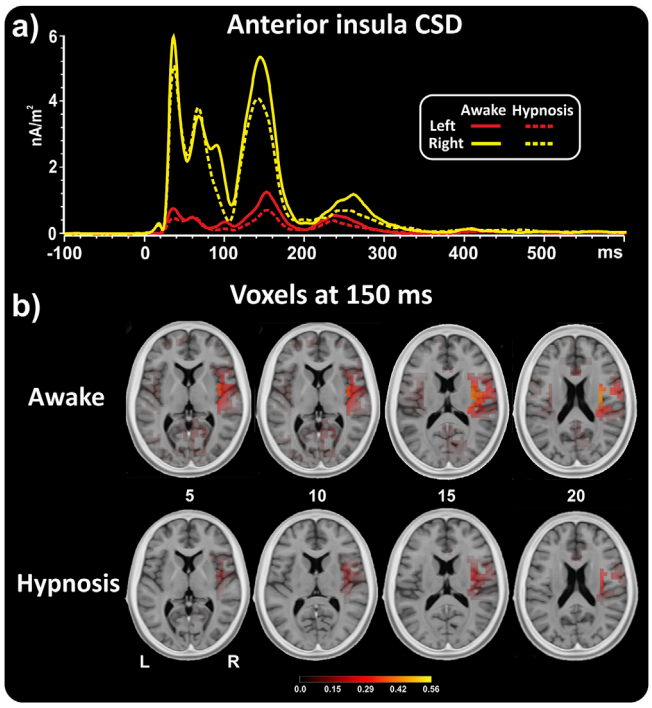


**Figure 6.** a) sLORETA-based current source density (CSD) waveforms of the right and left anterior insula in the two conditions. b) activation of voxels at 150 ms in the awake and hypnosis conditions.

The P150 emerged on the frontal-medial areas of the scalp: to the best of our knowledge, Zeng et al. (2006) were the only ones to describe this component, even if in the context of acupuncture stimulation. By fitting a single dipole, authors localized the anterior cingulate cortex (ACC) as the source of this component, which increased with the increased sensation scores. The present neuroelectric source analysis of the P150 revealed activity in frontoparietal brain areas, including the ACC and the right anterior insula (see Fig. 5). Findings of the present source analysis are in line with literature documenting the key role of the anterior insula in the consciousness of perception (for a review see Craig, 2010). Along this line, we suggest that somatosensory P150 might be assimilated to the prefrontal ERPs from the anterior insula associated with the perceptual awareness in the visual domain (i.e., the pP1 component; Perri et al., 2014, 2015, 2017, 2018a,b, 2019; Perri and Di Russo, 2017; Di Russo et al., 2017, 2019). These "visual" prefrontal components usually emerge on the AFz site, and the fMRI localized them in the rostral portion of the anterior insula (Di Russo et al., 2016): this might explain why their scalp distribution is slightly more anterior than the present P150 (i.e., the P150 was largest at FCz, see Fig. 4b). Further support to this explanation comes from studies indicating that sensorimotor and interoceptive signals are processed more posteriorly in the insular cortex (Craig, 2002; Droutman et al., 2015). The presence of asymmetric insular activity (strong on the right and really small on the left), likely is not due the left-sided stimulation because the right insula dominance resulted independent of the stimulated side (Di Russo et al., 2016; Sulpizio et al., 2017). In other words, this finding is in line with the key role of the right anterior insula in the perceptual- and self-awareness (for reviews see Craig, 2002, 2010; Karnath and Baier, 2010; Sterzer and Kleinschmidt, 2010), and we suggest that P150 represents the main ERP correlate of somatosensory conscious perception, while the P100 is a prerequisite for consciousness as it reflects processes of spatial selective attention from the parietal cortex (Dehaene and Naccache, 2001; Schubert et al., 2006). Nevertheless, inferences about neurophysiology of stimulus consciousness remains partly hypothetical as only trial-by-trial analysis could theoretically indicate the direct relationship between ERPs and subjective experience.

As for the P250, Simonsen et al. (2010) localized its source in the dorsal ACC and reported a reduced amplitude during the performance of a cognitive task compared with the neutral condition. The authors proposed an attentional account for this component and hypothesized it can be assimilated to the P300 described elsewhere. On the other hand, Shimojo et al. (2000) reported partial correlations between the amplitude of the P250 and the subjective ratings depending on the type of stimulation (skin or muscle). In the present study, this central distributed component was reduced in hypnosis, and source analysis on this activity suggested the contribution from generators located in the medial frontal gyrus and the dorsal regions of the cingulate cortex, typically considered as the "cognitive division" of the cingulate functioning (for a review seeBush et al., 2000). It is noteworthy that modulation of the P250 in the visual domain was associated with the attention allocated to emotional stimuli (Krusemark and Li, 2011) and the level of perceived distortion (Burkhardt et al., 2010), suggesting its contribution in the attentional processing. Even more interesting, studies with painful somatosensory stimuli demonstrated that hypnotic analgesia reduced the P250 as an effect of changes in the perception of intensity (for a review see Crawford et al., 1998). Together with present findings revealing a correlation between the P250 amplitude and the affective rating (i.e., the greater the reduction of unpleasantness in hypnosis, the smaller the P250), these evidence suggest that P250 might reflect the later stage of somatosensory perception associated with the affective integration of the sensory inputs. However, as literature on the somatosensory P250 is still scarce, these conclusions should be taken with caution and future studies are needed to clarify the specific role of this component in the neurophysiological and subjective processing of somatosensory stimuli.

### 4.4. Limitations

The main advantage of this study was to describe very suitable ERP findings in a large group of participants who received stimulation in different conditions. However, the present study is not exempt from limits: for example, we did not investigate the effects of suggestions outside of hypnosis. In fact, even if we asked participants to close their eyes and relax their mind in the awake condition, more focused suggestions of hypoesthesia were administered in hypnosis condition. Also, the absence of very Low-susceptible individuals did not allow to conclude whether hypnotic hypoesthesia was effective for this minority as well. Finally, as subjects were asked to rate their sensory and affective experience (VAS) after 18 min of stimulation, we cannot exclude that this might have introduced some bias of habituation.

## 5. Conclusions

The present study showed that hypnosis with suggestions of hypoesthesia reduces the perceived intensity and unpleasantness of the somatosensory non-painful stimulation and that these effects are associated

**Table 4**
Mean amplitudes of the main SEPs for the three subgroups of susceptibility (HGSHS). A = awake, H = hypnosis, Diff = differential.

| HGSHS | N20 | | | P100 | | | P150 | | | P250 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | H | Diff | A | H | Diff | A | H | Diff | A | H | Diff |
| High | −1.8 | −0.7 | −1.1 | 2.1 | 1.2 | 0.8 | 2.1 | 1.7 | 0.3 | 2.2 | 1.7 | 0.5 |
| Medium | −1.2 | −0.9 | −0.3 | 2.2 | 1.5 | 0.7 | 3.1 | 2.5 | 0.6 | 2.7 | 2.2 | 0.4 |
| Low | −1.2 | −0.9 | −0.3 | 1.8 | 1.0 | 0.8 | 2.6 | 1.9 | 0.7 | 1.3 | 0.8 | 0.4 |

with specific neurophysiological activities. Specifically, we found a hypnosis-related decrease of activity in cortical and limbic areas associated to early and late SEP components, such as the contralateral SI (N20), SII (P100), right anterior insula (P150) and cingulate cortex (P150/P250). We propose that modulations in these SEPs (and the related areas) should not be considered separately but reflect the activity of a neural network responsible for the somatosensory perception. In fact, anatomical connections between SI, SII, ACC and insula (Mufson and Mesulam, 1982; Friedman et al., 1986; Vogt and Pandya, 1987) suggest that they interact to encode different aspects of sensory and affective stages of processing (Rainville et al., 1997). These findings were never reported before in an ERP study but are in line with neuroimaging investigations indicating reduced activity in the same brain areas as an effect of hypnotic suggestions (for a review see Vanhaudenhuyse et al., 2014). Moreover, it was also suggested that hypnosedation act by through top-down modulation as hypnosis increases functional connectivity between SI and insular and prefrontal cortices (Vanhaudenhuyse et al., 2009).

Differently from previous neurophysiological studies of hypnosis, we adopted a correlational instead of a categorical approach: in other terms, participants were not selected on their high responsiveness to hypnosis, but they fall mostly into the medium range of susceptibility. However, in order to look at a possible effect of hypnotizability, we also presented descriptive statistics in the subgroups of High-, Medium- and Low-hypnotizable participants (see Section 3.3). The data would suggest that hypnotic hypoesthesia decreased the subjective ratings of Medium and Lows even more than Highs. Nevertheless, because of the small samples size, and the absence of very Low-susceptible (i.e., their mean HGSHS score was 4.8), these data can not be considered as very representative or suitable for statistical comparisons. Anyhow, present findings suggest the need of a new approach for the research in this field: indeed, as present effects were not specific for Highs, it will be needed for future investigations to do not exclude subjects with a medium level of hypnotizability (see also Jensen et al., 2017 on this point).

We adopted the Harvard Group Scale for measuring the individual susceptibility to hypnosis, while the individual Stanford Hypnotic Susceptibility Scales (SHSS:A; Weitzenhoffer and Hilgard, 1962) is more often adopted in these studies. One could argue that HGSHS:A is a less sensitive measure, and this might also explain why individual scores of susceptibility did not correlate with any of the neurophysiological measures. However, this hypothesis is unlikely as it was shown that HGSHS:A yields a measure of hypnotizability largely comparable to that obtained with the SHSS:A (De Pascalis et al., 2000). As an alternative explanation, we suggest that the standardized measures of susceptibility do not always catch the complex interaction of factors subtending the hypnotic effects in a sample of Medium, while they are more reliable when considering the Highs vs. Lows dichotomy.

As regards the association between neurophysiological data and subjective reports, we only found a significant correlation for the P250 component, that decreased together with a decrease in the perceived unpleasantness of the stimuli. No other SEP modulations correlated with the subjective ratings on the sensory and affective VAS: this finding would further confirm that subjective perception of somatosensory signals does not rely on a single neural activity but depends on different stages of processing of a network of cortical and subcortical regions.

Concluding, the present study showed that hypnosis modulates somatosensory perception since the earliest processing of the thalamocortical radiations, and not only in the later stages of affective integration as shown by previous investigations on pain. In other words, according to the main models of attentional control (for review see Awh et al., 2012), hypnosis can be defined as a top-down intervention of hypoesthesia in the sense that it reflects an endogenous, subject-driven (and not stimulus-driven or bottom-up) locus of control. Further, present findings indicate that hypnotic hypoesthesia was not specific for High-susceptible individuals, but it may represent a cost-effective tool for reducing sensory distress in the majority of the population.

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## Declarations of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116104.

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