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Perception and modulation of pain in waking and hypnosis: functional significance of phase-ordered gamma oscillations

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Abstract

Somatosensory event-related phase-ordered gamma oscillations (40-Hz) to electric painful standard stimuli under an odd-ball paradigm were analyzed in 13 high, 13 medium, and 12 low hypnotizable subjects during waking, hypnosis, and post-hypnosis conditions. During these conditions, subjects received a suggestion of Focused Analgesia to produce an obstructive hallucination of stimulus perception; a No-Analgesia treatment served as a control. After hypnosis, a post-hypnotic suggestion was given to draw waking subjects into a deep hypnosis with opened eyes. High hypnotizables, compared to medium and low ones, experienced significant pain and distress reductions for Focused Analgesia during hypnosis and, to a greater extent, during post-hypnosis condition. Correlational analysis of EEG sweeps of each individual revealed brief intervals of phase ordering of gamma patterns, preceding and following stimulus onset, lasting approximately six periods. High and medium hypnotizable subjects showed significant reductions in phase-ordered gamma patterns for Focused Analgesia during hypnosis and post-hypnosis conditions; this effect was found, however, more pronounced in high hypnotizable subjects. Phase-ordered gamma scores over central scalp site predicted subject pain ratings across Waking-Pain and Waking-Analgesia conditions, while phase-ordered gamma scores over frontal scalp site predicted pain ratings during post-hypnosis analgesia condition. During waking conditions, this relationship was present in high, low and medium hypnotizable subjects and was independent of stimulus intensity measures. This relationship was unchanged by hypnosis induction in the low hypnotizable subjects, but not present in the high and medium ones during hypnosis, suggesting that hypnosis interferes with phase-ordered gamma and pain relationship.
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1. Introduction

The present study examined the relationship between pain perception and EEG responses within the gamma band (38–42 Hz) by measuring stimulus evoked phase-ordered gamma patterns with a correlational method recently developed by Maltseva et al. (2000).

Gamma activity is thought to play an integral role in information processing (Karakas and Basar, 1998). Among different types gamma activity: spontaneous, evoked, induced and emitted (Galambos, 1992), the evoked gamma activity has been widely studied. This activity occurs after stimulus presentation as a phase-locked activity in the early time window of 0–150 ms. It is thought to reflect early processing of stimulus information (e.g. Basar et al., 1987; Basar and Demiralp, 1995; Galambos et al., 1981; Llinas and Ribary, 1992; Pantev et al., 1991). But there is experimental evidence that synchronized gamma activity is also involved in selective attention. Evoked gamma activity (peaking at about 30 and 100 ms) was also found to increase during task requiring to direct attention to tones presented in one ear while ignoring tones being presented to the other ear (Tiitinen et al., 1993, 1997).

Recently, spatio-temporal dynamics of the event-related oscillations in different EEG bands between painful and non-painful somatosensory stimulation was studied by Chen and Hermann (2001). Later, Babiloni et al. (2002), using fine spatial-analysis of the EEG oscillations, has evidenced that galvanic painful stimulation, compared to non-painful stimulation, increased phase-locked theta to gamma band

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responses in the contralateral hemisphere and decreased the phase-locked beta band response in the ipsilateral hemisphere. Tecchio et al. (2003), using somatosensory neuromagnetic fields, provided experimental evidence that neural synchronization in somatosensory cortex (S1) may vary in frequency as a function of the stimulated finger (i.e. increments of beta (20–32 Hz) event-related coherence after little finger stimulation and of gamma (36–44 Hz) after the thumb stimulation).

Croft et al. (2002) conducted a study in which EEG spectral power (8–100 Hz range) was measured to painful electric stimuli delivered using an odd-ball paradigm. Gamma activity (32–100 Hz) over prefrontal scalp sites predicted subject pain ratings in the control condition. This relation was found unchanged by hypnosis in low hypnotizables while it was lacking during hypnosis and hypnotic analgesia in high hypnotizable subjects, suggesting that hypnosis interferes with this pain-gamma relationship.

In the present study, measures of phase-ordered gamma patterns, evoked by painful standard electric stimuli, and perceived stimulus intensity were obtained while subjects were engaged in a somatosensory oddball task. The study used a Focused Analgesia protocol requiring to produce an obstructive image of incoming stimuli that, in previous studies, was proved to be effective in pain relief (De Pascalis et al., 1999, 2001; Zachariae and Bjerring, 1994). This treatment was suggested in waking, hypnosis and a post-hypnotic suggestion conditions. Aim of the study was to determine whether: (1) phase-ordered gamma oscillation is a reliable indicator of pain sensation; (2) individual differences in hypnotic susceptibility reliably account for more pronounced pain reduction during hypnotic analgesia; (3) pain reduction is paralleled by reduction in the degree of phase-ordered gamma responses.

2. Methods

2.1. Subjects

The subjects were 38 right-handed undergraduate students (20 women and 18 men; age range 19–30 yr) pre-selected for high ($N=13$; 7 women and 6 men), medium ($N=13$; 7 women and 6 men), and low ($N=12$; 6 women and 6 men) levels of hypnotic susceptibility. The subjects were tested using the Stanford Hypnotic Susceptibility Scale, Form C (SHSS:C; Weitzenhoffer and Hilgard, 1962). The participants were categorized as being high hypnotizable subjects ($N=13$, $M=9.9$, SD $=0.86$) when their scores on SHSS:C were 1 SD above the group mean of a larger sample of 78 subjects tested in our department ($N=48$ women and 30 male, $M=6.0$, SD $=2.96$); an equivalent but opposite deviation designated the low hypnotizable subjects ($N=12$, $M=2.8$, SD $=1.47$). The moderately hypnotizable group was formed with subjects who showed hypnotizability scores 1 SD within the group mean ($N=13$, $M=6.1$, SD $=0.9$). Three different female hypnotists and one male hypnotist carried out the assessment of hypnotic susceptibility about 1 month prior to the second session. During this session, hypnosis was induced by one of the four hypnotists who did not know the hypnotizability level of the subject. All subjects were unacquainted with their hypnotic ability and care was taken to ensure that they had no awareness of the relevance of hypnotic ability to their participation in the experiment. Women who were in a menstrual period were invited for EEG recordings in another occasion, because menstrual cycle has been known to affect EEG activity (e.g. Glass, 1968). Subjects were admitted to participate in the experiment only if they reported an absence of medication use (e.g. psychoactive drugs, antihistamines, and anti-inflammatory medications) or medical conditions that might interfere with pain sensitivity (e.g. high blood pressure, diabetes mellitus, heart diseases, asthma, Raynaud's syndrome, frostbite, arthritis, post trauma to hands).

2.2. Procedure

The subjects were seen individually in the lab and upon arrival they were informed about the nature of the painful electric stimulation. Written consent was obtained if they agreed to continue with the study that was conducted according to the ethical norms of the Italian Association of Psychology (AIP). On this occasion, hypnosis was induced for the second time using the Stanford Hypnotic Clinical Scale (SHSC; Morgan and Hilgard, 1978–1979). The subjects were all naïve volunteers and not informed about their hypnotizability level during the EEG recording session.

2.2.1. Pain treatment conditions

The subjects were engaged in five pain treatment conditions: (1) Awake-Pain; (2) Focused Analgesia in waking state; (3) Hypnosis-Pain; (4) Focused Analgesia in hypnosis; and (5) Post-hypnosis suggestion of analgesia. At the end of hypnosis condition, the subject received a suggestion that during waking state after hypnosis, he/she will enter again in hypnosis with opened eyes after that the experimenter will have knocked two times on the wall. Both waking and the hypnosis conditions were counterbalanced across subjects in order to avoid possible sequence effects or habituation. However, within waking and hypnosis conditions, task order was not varied and painful condition was always administered first. Between waking and hypnosis conditions a resting period of 15 min was given. In each treatment condition (lasting about 5 min), painful stimuli were applied to the subjects and, at the end of each condition, they were asked to rate any pain and distress experienced for standard stimuli on two separate 10 point numeric rating scales (NRS; Jensen et al., 1986). On the left and right sides of the NRS-sensory scale, there were,

respectively, the descriptors '0 = no pain sensation' and '10 = the most pain sensation imaginable'. Similarly, on the left and right sides of the NRS-distress scale, there were, respectively, the descriptors '0 = not at all distressful and the most distressful imaginable'. An involuntariness measure of pain reduction effect was obtained at the end of Post-Hypnosis-Analgesia condition by requiring participants to rate on the NRS how much they experienced pain reduction as occurring as involuntarily (0 = quite voluntarily and 10 = absolutely involuntarily). The suggestions used in the experimental session were as follows:

(1) *Waking-Pain* (W-Pain)—No suggestions attempting to reduce pain were given, it was only required to detect target painful stimuli (eyes-open);
(2) *Waking-Analgesia* (W-Analgesia)—Suggestions to enter into a relaxed condition accompanied by a suggestion 'to focus on sensation in the finger and hand and to experience that all sensations of the stimulated finger will be attenuated 'as if it was a glove' that was covering the finger and the hand' (eyes-open);
(3) *Hypnosis-Pain* (Hy-Pain)—Following hypnotic induction, painful stimuli were delivered without suggestions attempting to reduce pain (eyes-closed);
(4) *Hypnosis-Analgesia* (Hy-Analgesia)—During hypnosis a Focused Analgesia suggestion, as in (2), was given (eyes-closed);
(5) *Post-hypnosis-Analgesia* (P.Hy-Analgesia)—After hypnosis condition subject was suggested to enter again in a state of hypnosis with eyes-open wherein a Focused Analgesia suggestion, as in (2), was administered.

In each condition, the subject was asked to count the number of delivered target stimuli.

2.2.2. Measure of sensory and pain tolerability thresholds

The electric stimulus was applied using two silver–silver chloride cup electrodes to a target area on the centers of palmar surfaces of the distal and medial phalanges of the middle finger of the right hand. Palmar surface of the finger was prepared by rigorously rubbing with an alcohol swab. Electrode cup (1 cm in diameter) was filled by an electroconductive ipoallergic cream and impedance was checked before EEG recording and kept below 30 kΩ. Stimuli consisted of unipolar electrical pulses of 2 ms duration, generated by a constant current stimulator (Digimiter, Mod DS7A). For each subject, before each experimental condition, measures of sensory threshold and of pain threshold were obtained. The sensory threshold was defined as the intensity of current stimulation (mA) that the subject perceived as a 'detectable pin-prick', and the pain threshold as a 'distinct sharp painful pin-prick'. Sensory threshold was established by delivering a number of stimuli of increasing intensity using steps of 0.05 mA. The first stimulus was of 0.05 mA and the others were delivered in ascending levels of stimulation with an interstimulus interval of approximately 10 s. The subject was required to indicate the stimulus in which he/she perceived the pin-prick as the minimum detectable pin-prick. Pain tolerability threshold was determined (just after the measure of sensory threshold) by delivering stimuli of increasing intensity, using steps of 0.5 mA, as the maximum perceptible painful pin-prick. After this level, stimulus intensity was then increased until the subject reported the delivered stimulus as very painful, above which there would be the greatest pain sensation imaginable. This value was considered as the pain intolerability threshold and stimulus intensity used throughout all experimental conditions was kept 0.5 mA under the individual pain intolerability threshold. Pain and sensory thresholds were determined just before the EEG recordings.

2.2.3. Electric pulse stimulation

For each experimental condition the subjects completed a block of 70 electrical stimuli delivered using an oddball paradigm. Infrequent targets (14.5%) were interspersed among frequently occurring standard stimuli (85.5%). Target presentation order was pseudorandomized and met the criteria that two targets were not presented in succession. The inter-stimulus interval was set at a constant time of 3 s. Each standard stimulus consisted of one unipolar pulse with a duration of 2 ms. Target stimulus was formed by pairing two standard stimuli with an inter-pulse interval of 25 ms.

2.3. EEG data acquisition and processing

EEG recordings were made using an Electro-cap (Blom and Anneveldt, 1982) with pure tin electrodes placed on frontal (F3, F4), parietal (P3, P4) and midline (Fz, Cz, Pz) sites. Linked earlobes served as reference with a forehead ground. Electrode impedance was kept below 3 kΩ and raw EEG signals were recorded (0.3 s time constant) using an eight-channel EEG machine ('ERA-9'—OTE Biomedica Italiana, 75 Hz cutoff). Eye movement (EOG) was recorded in a bipolar arrangement, superior orbit referenced to the outer canthus of the left eye. The EEG was acquired in digital form, using an IBM-compatible computer, by sampling at 1024 Hz per channel with a 12-bit resolution (Metrabyte Dash-16). For each instruction condition, 70 epochs (60 for standard and 10 for target stimuli) were digitized and stored on hard disk, using a time period of 500 ms prior and 500 ms after stimulus onset. Trials with artifacts due to scalp muscle or stimulus contamination, head or electrode movement, or eye-movement slow potential variations (EEG $>100\,\mu V$) were a posteriori eliminated. For further off-line analysis only EEG sweeps corresponding to standard stimuli were analyzed. This was done since there is experimental evidence that standard stimuli are more probable to elicit a 'pain-specific' event-related response that is more dependent from nociceptive component of the stimulus less influenced by the cognitive

information processing not intrinsic to pain (Becker et al., 1993, 2000).

The EEG was digitally filtered without phase shift (FIR filter) in the gamma band (38–42 Hz). To control for electromiographic (EMG) contamination from scalp muscle, the EEG signal for each electrode was filtered offline into a 62–75 Hz band (EMG) and the EEG-gamma values were corrected by using a linear regression of the EEG-gamma on EMG values. The following correction was used: (Corrected EEG-gamma) $=y-(\sum xy/\sum x^2)x$ where x equals measured EMG activity and y equals measured EEG-gamma activity. For determination of phase-ordered gamma patterns, a correlation analysis method, developed by Maltseva et al. (2000) for alpha oscillations, was used to estimate the similarity of the dynamics of the specificity of phase-ordered oscillations with stimulus onset (for more details, see Maltseva et al., 2000). The data of each subject contained four sets of 15 sweeps for each experimental condition and each channel.

2.4. Statistical evaluation

Correlation analysis was used for statistical estimation of the covariance of gamma oscillations within each subset of 15 sweeps. The covariance of oscillations in each subset of 15 sweeps was estimated within a 150 ms time window which was shifted along the time axis in steps of 15 ms. For example, the interval from −375 to −225 ms for each of 15 sweeps was presented by a discrete time series at the amplitudes A_t, $t=1,2,3,\ldots,150$. Correlation coefficients were computed for each pairwise combination of such time series. That means that 105 correlation coefficients were obtained. They were converted into Fisher's Z-values $Z_{nk}=1/2\ \ln[(1+r_{nk})/(1-r_{nk})]$ and then averaged. The mean of Z values was used as a measure of similarity of gamma oscillation responses in the time interval of analysis. The same procedure was applied to intervals from −225 to −75 ms, from −75 to 75 ms, etc. up to the last interval from 345 to 495 ms. From this analysis 59 estimates of mean Z values were obtained for each subset of sweeps. These values reflect the dynamic of intersweep relationships for gamma oscillations as a function of time. This method is illustrated in Fig. 1 wherein Z values are plotted against the onset of the painful stimulus ($t=0$). The figure shows that when the oscillations are phase-aligned the mean Z values increase, while Z values near to 0 indicate that oscillations have an accidental behavior in the part of superimposed sweeps. For further analyses, one set of sweeps for each experimental condition was selected for each subject. Visual inspection of phase-ordered gamma patterns disclosed that the most pronounced significant phase ordered gamma oscillations were across Fz and Cz sites. Thus, the set of sweeps showing the highest peak of mean Z values to at least in one of the midline recording sites (Fz, Cz, Pz), was considered to be the set with the most marked phase tuning. This set of sweeps was considered for comparison with

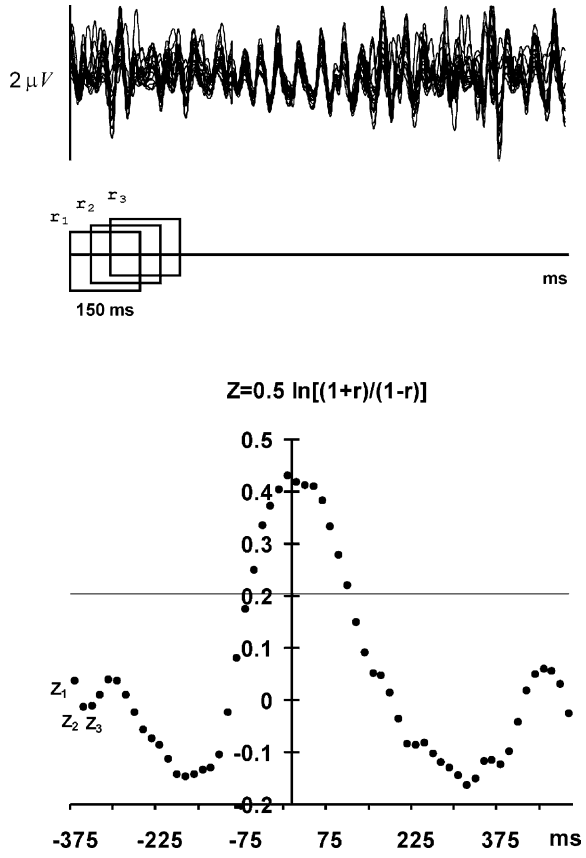

Fig. 1. Correlational method of estimation of intersweep congruence. Mean correlation coefficients between sweeps (Z_1, Z_2, Z_3) are computed after Fisher's Z-transform in a time window of 150 ms shifted with steps of 15 ms.

the behavioral data. The relationship between phase-ordered gamma oscillations between sweeps can be considered as significant if the Z value obtained in the 150 ms interval exceeded the critical Z value of $Z=0.211$, that is corresponding to the critical Pearson correlation coefficient of $r=0.208$, for $n=150$ and $P=0.01$. In Fig. 1 it can clearly seen that phase-aligned oscillations are apparent before stimulus onset and by reaching a maximum peak at around stimulus onset. For each experimental condition, the maximum peak value of the Z curve in the time interval of analysis were collected and used as dataset for further analyses. For these data scores repeated measures ANOVAs were performed using the following design: three groups of 'Hypnotizability' (high, medium, low) ×3 'Location' (Fz, Cz, Pz) ×5 'Levels of condition' (Awake-Pain, Waking-Analgesia, Hypnosis-Pain, Hypnosis-Analgesia, Post-hypnotic-Analgesia). Similar ANOVAs were performed for behavioral data scores.

Significant levels of F tests were adjusted using the Greenhouse–Geisser epsilon in cases where the sphericity was violated. Post-hoc comparisons were performed using a t-test procedure. Finally, multiple regression analyses were performed to evaluate the relationship between phase-ordered gamma scores and pain intensity ratings.

3. Results

3.1. Pain and distress ratings

Both pain and distress rating scores displayed a main effect for 'Condition' ($F_{4,140}=7.18$, $p=0.0005$; $F_{4,140}=8.29$, $p=0.0002$; for pain and distress scores, respectively). This effect indicated that during Hy-Analgesia and, even more, P.Hy -Analgesia conditions there were significant reductions in pain and distress levels compared with W-Pain and Hy-Pain conditions (t-test, $p<0.05$). The interaction of 'Hypnotizability' × 'Condition' was also significant for pain ratings ($F_{8,140}=2.78$, $p=0.0214$) and distress ratings ($F_{8,140}=2.60$, $p=0.0280$). This interaction indicated that, compared with moderately and low hypnotizable subjects, the high hypnotizable subjects obtained more pronounced decreases in pain and distress sensations during Hy-Analgesia and, in a more pronounced way, during P.Hy-Analgesia treatment. These effects are clearly displayed in Fig. 2.

3.2. Stimulus settings and involuntariness ratings

Separate ANOVAs were performed for sensory threshold, pain and distress thresholds, stimulus intensity and involuntariness rating scores. With the exception of involuntariness scores, each of these analyses failed to evidence differences among hypnotizability groups ($p>0.05$).

The ANOVA for involuntariness ratings found a main effect for hypnotizability ($F_{2,35}=5.52$, $p=0.0083$). This effect indicated that high hypnotizable individuals reported higher involuntariness scores for pain reduction during P.Hy-Analgesia than did medium and low hypnotizable subjects (7.3, 4.4, and 4.0, respectively).

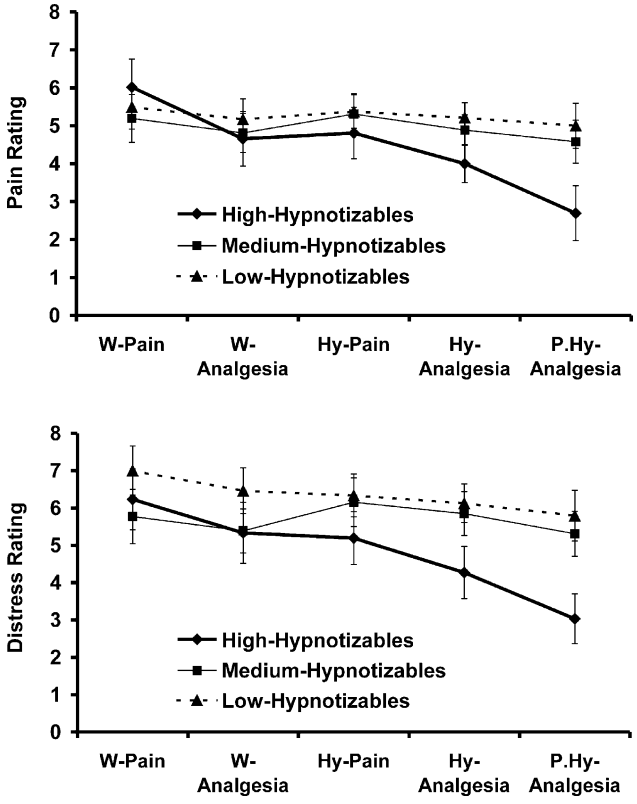

Fig. 2. Mean sensory pain and distress ratings (±SE) to standard stimuli in 13 high, 13 moderately, and 12 low hypnotizable subjects (high, medium, and low). Measures were obtained during the following conditions: Waking-Pain, Waking-Analgesia, Hypnosis-Pain, Hypnosis-Analgesia, Post-Hypnosis-Analgesia

3.3. Phase-ordered gamma scores

The ANOVA for Z peak values of phase-ordered gamma patterns evidenced the following effects: (1) Location ($F_{2,70}=48.47$, $p<0.0001$); (2) Condition ($F_{4,140}=9.25$, $p<0.0001$); (3) Hypnotizability ($F_{2,35}=10.42$, $p=0.0003$); (4) Condition × Location ($F_{8,280}=3.40$, $p=0.0038$); (5) Hypnotizability × Location ($F_{4,70}=4.22$, $p=0.0045$); (6) Hypnotizability × Condition ($F_{8,140}=4.48$, $p=0.0002$); (7) Hypnotizability × Location × Condition ($F_{16,280}=3.94$, $p<0.0001$).

The first effect indicated that there were more pronounced Z peak scores of phase ordered gamma patterns over the recording sites of Fz and Cz as compared to Pz (0.25, 0.31, and 0.18, respectively). The second effect displayed that during W-Analgesia, Hy-Analgesia, and P.Hy-Analgesia conditions there were smaller peaks of phase ordered gamma patterns as compared to W-Pain and Hy-Pain conditions (0.24, 0.22, and 0.20 vs. 0.30 and 0.28, respectively). The last three effects indicated that high hypnotizable subjects, across Fz and Cz leads, during Hy-Analgesia and P.Hy-Analgesia conditions, produced significant peak reductions of phase-ordered gamma patterns as compared to the remaining conditions. The W-Analgesia condition also displayed a significant reduction, but it was less pronounced compared to analgesia treatment conditions. Medium hypnotizable subjects, during analgesia treatments conditions, also showed similar patterns of phase-ordered gamma reductions over Fz and to a less extent over Cz leads, but, for these subjects, the W-Analgesia treatment showed a more pronounced reduction as compared to Hy-Analgesia condition. Low hypnotizable subjects, in contrast to the other groups, did not display parallel patterns of phase-ordered gamma reductions over Fz and Cz sites during experimental conditions. Midline phase ordered gamma patterns across conditions for each hypnotizability group are displayed in Fig. 3.

3.4. Pain intensity and phase-ordered gamma scores

Stepwise multiple regression was used to determine if phase-ordered gamma scores over any of the seven regions of the scalp was related to pain ratings. This involved one regression for each experimental condition, where seven scalp regions served as predictor variables and pain ratings the criterion variable. A significance level of 0.05 for inclusion and a significance level of 0.10 for exclusion in

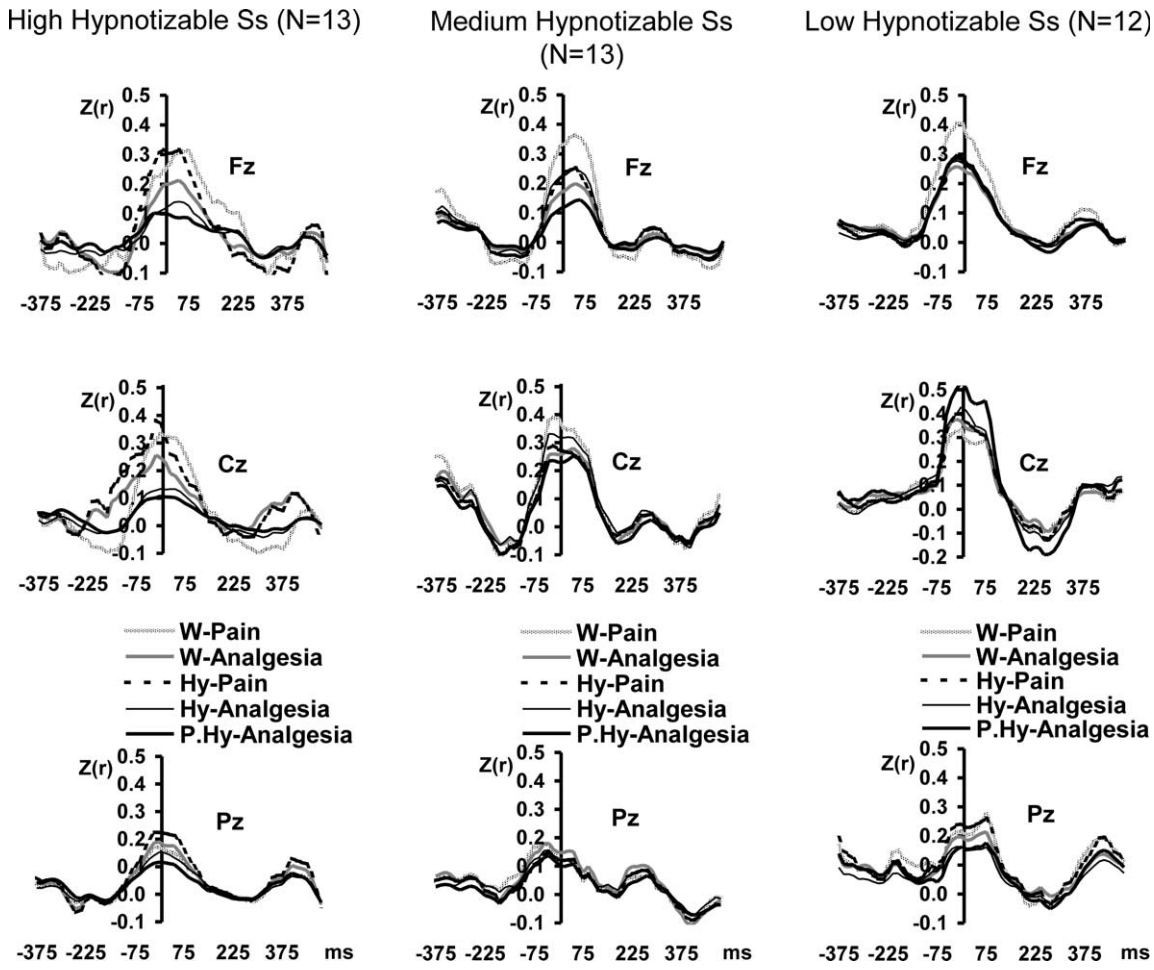

Fig. 3. Dynamics of averaged intersweep correlations of phase-ordered gamma patterns at Fz, Cz and Pz recording sites in high, medium, and low hypnotizable subjects during waking (W-Pain, W-Analgesia) and hypnosis (Hy-Pain, Hy-Analgesia, P.Hy-Analgesia) conditions.

the model were used for each regression. Phase-ordered gamma scores over Cz scalp site predicted pain intensity across the two waking conditions (W-Pain: $B=18.81$, $F_{1,36}=52.44$, $p<0.0001$; W-Analgesia: $B=13.63$, $F_{1,36}=41.92$, $p<0.0001$). The Hy-Pain and Hy-Analgesia conditions failed to evidence any gamma predictor of pain intensity ($p>0.05$). In contrast, during P.Hy-Analgesia condition (subject with eyes-open) gamma scores over Fz scalp site predicted pain ratings ($B=7.46$, $F_{1,36}=14.86$, $p=0.0005$).

To determine whether this gamma/pain relationship was independent of stimulus perception and pain/distress thresholds, for each condition separate multiple regression analyses were used. Predictor variables were 'phase-ordered gamma scores' (at Cz for waking conditions and at Fz for P.Hy-Analgesia condition), 'sensory threshold', 'pain threshold', 'distress threshold', and 'stimulus intensity' (mA). Criterion variable was 'pain intensity ratings'. Independently of the other variables, phase-ordered gamma score at Cz scalp location was the best predictor of 'pain ratings' for waking conditions (W-Pain: $B=11.02$, $t=6.17$, $p<0.0001$; W-Analgesia: $B=11.42$, $t=5.81$, $p<0.0001$). No significant predictors were found for Hy-Pain and for Hy-Analgesia ($t<2.03$, $p>0.05$). Frontal gamma score was the best predictor of pain rating during P.Hy-Analgesia ($B=5.91797$ $t=2.67$ $p=0.0118$) and none of the other variables independently predicted pain ratings ($t<1.85$, $p>0.07$).

To determine the internal consistency of the relationship between pain ratings and phase-ordered gamma scores and whether this relationship held during waking and hypnosis conditions, simple regressions were performed for high, medium, and low hypnotizable subjects separately for each experimental condition, where phase-ordered gamma score was the predictor and pain rating the criterion variable. As can be seen in Fig.4, central gamma scores predicted pain ratings similarly across high, medium, and low hypnotizables for W-Pain condition (High-hypnotizables: $B=13.92$, $t=4.22$, $p=0.0014$; Medium-hypnotizables: $B=12.59$, $t=3.82$, $p=0.0028$; Low-hypnotizables: $B=12.37$, $t=4.20$, $p=0.0018$). Similar relationships were obtained across hypnotizability groups for W-Analgesia condition (High-hypnotizables: $B=13.98$, $t=3.7$, $p=0.00333$; Medium-hypnotizables: $B=11.02$, $t=2.45$, $p=0.032$;

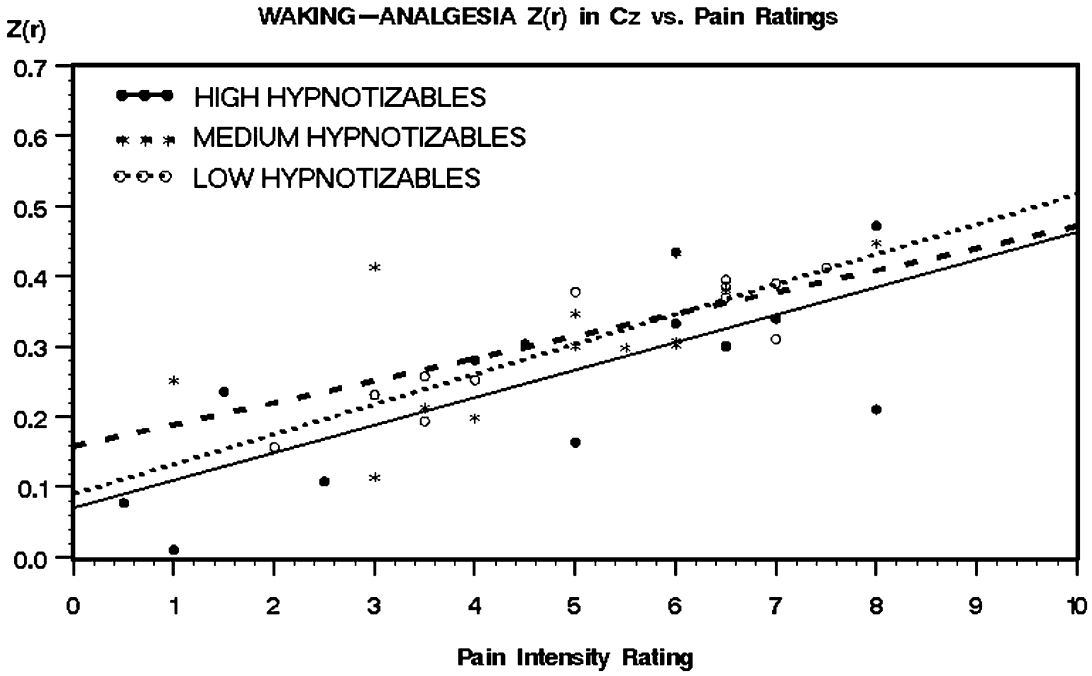

Fig. 4. The relationship between subject's central phase-ordered gamma scores and their reported pain levels are shown during waking pain (W-Pain) condition for the high (solid line), medium (dashed line) and low (dotted line) hypnotizable subjects separately.

Low-hypnotizables: $B=18.80$, $t=6.73$, $p<0.0001$). Importantly, during Hy-Pain and Hy-Analgesia conditions, high and medium hypnotizables failed to evidence any significant relationship ($t<1.5$, $p>0.15$). However, during P.Hy-Analgesia gamma scores at Fz predicted pain ratings for t values that were near the significance levels (High-hypnotizables: $B=4.80$, $t=2.02$, $p=0.068$; Medium-hypnotizables: $B=6.89$, $t=1.97$, $p=0.074$). For low hypnotizables gamma scores at Cz predicted pain ratings during Hy-Pain ($B=8.98$, $t=8.49$, $p<0.0001$) and Hy-Analgesia ($B=19.15$, $t=2.86$, $p=0.017$), while frontal (Fz) gamma scores predicted pain during P.Hy-Analgesia ($B=7.17$, $t=2.66$, $p=0.024$) conditions.

4. Discussion

Results from the present study have evidenced patterns of phase-ordered gamma activity across experimental pain conditions associated to the delivering of painful stimulation. These patterns represent the similarity (or covariance of wave shape) over EEG segments of approximately six periods of gamma rhythm. The phase-tuning mechanism of gamma activity was observed to start before the onset of painful stimulation (see Fig. 1). Considering that a fixed interstimulus interval was used, this anticipation-related change of activity can be attributable to the interplay of different processes such as coping with the impending stimulus and sustained attention mechanisms. Furthermore, this study has evidenced that the most pronounced gamma-tuning effects were over midline frontal (Fz) and central (Cz) scalp locations and that phase-ordered gamma activity over central scalp site (Cz) is the best predictor of subjective experience of pain. Importantly, this relationship was independent of stimulus parameters measures, suggesting that the relation was not due to increased general arousal following more painful stimulation, nor merely due to the stimulus intensity changes among subjects. Rather the gamma synchronization seems to reflect the engagement of a selective neural network including the central region of the cortex which is more linked to the activity for stimulus perception of the primary somatosensory cortex (S1). This interpretation appears consistent with a number of brain imaging findings. For example, anterior cingulate cortex (ACC) metabolism has been found to vary with within-subject pain report (Porro et al., 1998; Rainville et al., 1997); functional connectivity between midcingulate cortex and a number of cortical (insular, pregenual and frontal regions) and subcortical structures (brain stem, thalamus, and basal ganglia) has been found as responsible for hypnosis-related alteration of sensory and affective components of pain (Faymonville et al., 2003). The anticipation of phase tuning of gamma activity, observed in this study with painful stimulation, may imply that endogenous processes manifested by phase reordering of the gamma waves are strongly associated with cortical stimulus representation and probably reflect operations on memory traces of impending stimulation. This finding appears consistent with functional magnetic resonance imaging (fMRI) reports that expectation of pain activates cingulate and insular cortex (Ploghaus et al., 1999) and primary somatosensory cortex (Porro et al., 2002).

Further, that phase-ordered gamma band is related to pain perception is in line with research implicating gamma with subjective experience of pain. For example, gamma is reduced when people are anesthetized (Kulli and Koch, 1991) and gamma is increased in amplitude across prefrontal lobes (Croft et al., 2002), over somatosensory and prefrontal/parietal regions (Chen and Hermann, 2001), gamma synchronizes with electrical stimulation of the thumb in human primary somatosensory cortex as revealed by somatosensory evoked neuromagnetic fields (Tecchio et al., 2003), phased-locked gamma band responses are increased in the contralateral hemisphere during painful stimulation, compared to a nonpainful stimulation (Babiloni et al., 2002).

For the overall hypnotizability group, the relation between pain ratings and gamma over Cz scalp site was significant during waking treatments, while it was not present in both Hy-Pain and Hy-Analgesia conditions. Noteworthy, during post-hypnosis condition this relationship was found over Fz scalp site. That the relation between pain ratings and gamma was not present in both Hy-Pain and Hy-Analgesia conditions was mainly due to the contribution of high and medium hypnotizable individuals who, for these treatments, failed to evidence a significant gamma/pain relation. However, the fact that during Hy-Analgesia condition gamma/pain relation was not significant, while during P.Hy-Analgesia this relation was significant, may be seen as an apparent paradox given that both hypnosis conditions produced analgesia in high hypnotizables. These findings are not paradoxical since during P.Hy-Analgesia condition over Cz scalp site the gamma/pain relation, for the overall hypnotizability group, was also lacking as in the hypnosis condition, but it appeared to be significant over Fz scalp site. Separate regressions across hypnotizability groups indicated that this significant relation was due to the fact that for both high and medium hypnotizables the gamma/pain relationship for Fz scalp site was near to reach the significance levels, while for low hypnotizables was quite significant. Thus, the significant gamma/pain relation at Fz site, found during P.Hy-Analgesia, could indicates that in post-hypnosis condition the frontal lobe plays a new role in pain perception. In this condition, high hypnotizable individuals yielded the greatest reduction of gamma synchronization over frontal region, indicating that this region is more inhibited, a result which appears in line with the highest involuntariness levels and with the lower pain sensations observed in high hypnotizable individuals. Another reason of the frontal gamma/pain relationship during post-hypnosis treatment may lay in the fact that, in this condition, subjects had their eyes open during obstructive hallucination. Thus, a higher information input occurred simultaneously from internal and external sources while subjects experienced a higher level of involuntariness in pain reduction. This experience can be seen as the product of the inhibition of executive prefrontal functions (Hobson, 2000), an altered state of consciousness that is seen during hallucinations induced by hallucinogenic drugs (Farthing, 1992).

In sum, the present results support the view that hypnosis involves the suspension of high order attention system and other anterior executive functions (Crawford and Gruzelier, 1992; Woody and Bowers, 1994). This is because gamma synchronization decreased in the high and medium hypnotizable individuals during hypnosis, but it was no longer related to their subjective experience of pain. The pattern of our gamma/pain relationships appears quite similar to that evidenced by Croft et al. (2002) for prefrontal spectral gamma (32–100 Hz) amplitude. However, in the present study the most linked region to painful stimulation was in the central region of the scalp, a region more linked to the activity of primary somatosensory area. This is consistent with ERP results of Kakigi et al. (1996) who found negative components (N240 and N300) maximal at vertex in response to laser stimulation, a result that these researchers have seen as reflecting the activity of cingulate and subcortical areas. Similar conclusions were derived in terms of the N140 ERP component by Ray et al. (2002) using a dense array EEG procedure. The view that primary somatosensory cortex is important for the discrimination and modulation of various aspects of pain has been supported by lesions in animal and human findings (Bushnell et al., 1999). Furthermore, our gamma results indicate that hypnotic suggestions in high susceptible individuals modulate the activity of frontal and central areas of the cortex. It can be advanced that the mechanisms of this modulation for hypnotic analgesia suggestions includes inhibition of the sensory areas mediated by cortico-thalamic top-down projections. These early effects may be mediated by the level of activity of arousal structures such as the parts of the ascending reticular system or the thalamic intralaminar nuclei (Kinomura et al., 1996; Robbins, 1997).

There have been a number of experimental studies reporting that somatosensory ERPs following electrical stimulation of the medium nerve were markedly modified by voluntarily active movements of the fingers (‘gating effect’) that produce suppression of neural activity in sensory areas and reduced levels of conscious sensation (e.g. Haggard and Whitford, 2004; Giblin, 1964; Kakigi et al., 1995). Unfortunately, we did not monitor muscle tone in the district adjacent to the stimulated finger, thus we are unable to evaluate if pain application might have provoked a ‘sensory gating’ effect. However, considering that gamma/pain relation was independent from stimulus parameter measures and that there are no logical reasons to assume that ‘gating effect’ should be more pronounced in high hypnotizable individuals during hypnosis-analgesia conditions, we excluded that ‘gating effect’ may have caused the observed responses in this study.

Finally, ANOVA results of the present study have evidenced that high hypnotizable, but not medium and

low hypnotizable individuals, produced significant reductions of phase-ordered gamma scores over both frontal and central scalp sites during Hy-Analgesia and P.Hy-Analgesia conditions as compared to painful control conditions. Moreover, in high hypnotizables these reductions were found to be paralleled by significant reductions in pain and distress ratings. These and correlational results shed light not only on neural mechanisms involved in pain processing, but also on hypnosis processes. In particular, both support the view that hypnosis involves the suspension of a high order attention system (Crawford and Gruzelier, 1992; Woody and Bowers, 1994) and other executive functions (Croft et al., 2002; Gruzelier and Warren, 1993; Kallio et al., 2001; Nordby et al., 1999; Woody and Farvolden, 1998). These findings are also consistent with a number of psychophysiological studies reporting that perceptual alteration in hypnosis, as those of obstructive hallucination blocking the view of a visual stimulus (De Pascalis, 1994; Spiegel and Barabasz, 1988; Spiegel et al., 1985) or reducing the perception of noxious somatic stimulation (De Pascalis et al., 1999, 2001; Ray et al., 2002; Spiegel et al., 1989), is the product of a global inhibitory process involving not only late, but also early processes in the brain. Results from the present study appear in line with dissociated-control theory of hypnosis predicting that hypnotic analgesia responses are occurring to a more pronounced degree of involuntariness in hypnosis.

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