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Pain modulation as a function of hypnotizability: Diffuse noxious inhibitory control induced by cold pressor test vs explicit suggestions of analgesia

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HIGHLIGHTS

- Conditioned analgesia is studied in subjects (Ss) with different hypnotizability.
- Subjective and cardiac aspects are compared to suggestion-induced analgesia.
- Pain reduction is larger in high than in low hypnotizable Ss for both interventions.
- Medium hypnotizable Ss report intermediate pain reduction.
- Heart rate turbulence due to unconditioned stimuli are not significant.

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ABSTRACT

The aim of the present study was to compare the effects of explicit suggestions of analgesia and of the activation of the Diffuse Noxious Inhibitory Control (DNIC) by cold pressor test on pain perception and heart rate in healthy participants with high (highs, $N = 18$), low (lows, $N = 18$) and intermediate scores of hypnotizability (mediums, $N = 15$) out of hypnosis. Pain reports and the stimulus-locked heart rate changes induced by electrical nociceptive stimulation of the left hand were studied in the absence of concomitant stimuli (Control), during suggestions of analgesia (SUGG, glove analgesia) and during cold pressor test used as a conditioning stimulus to the right hand (DNIC, water temperature = 10–12 °C) in the REAL session. Participants were submitted also to a SHAM session in which the DNIC water temperature was 30 °C and the suggestions for analgesia were substituted with weather forecast information. Both suggestions and DNIC reduced pain significantly in all subjects; however, the percentage of reduction was significantly larger in highs (pain intensity = 55% of the control condition) than in mediums (70%) and lows (80%) independently of the REAL/SHAM session and of the specific pain manipulation. Heart rate was not modulated consistently with pain experience. Findings indicate that both suggestions and DNIC influence pain experience as a function of hypnotizability and suggest that both sensory and cognitive mechanisms co-operate in DNIC induced analgesia

1. Introduction

Non-pharmacological pain modulation can be achieved through cognitive and physical interventions. Among the former, the suggestions for analgesia (explicit requests to imagine to be protected against pain and/or being unable to feel pain) are known to reduce experimental pain in healthy individuals as well acute and chronic pain in patients both under hypnosis and in the ordinary state of consciousness [16,31]. The suggestions' efficacy is proportional to the subjects' level of hypnotisability [15,23,24,38,47], a physiological trait associated with the ability to modulate perception, memory and behaviour [64,65] and with a few sensory-motor and cardiovascular characteristics observable in the absence of hypnotic induction and specific suggestions [46].

Suggestion-induced analgesia is associated with the modulation of the activity/connectivity of the pain matrix [16,59] and is strictly

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dependent on the suggestions content, which may relate to the sensory and/or affective dimension of pain [22,42]. Suggestions influence also the nociceptive reflex [13,25,63], whereas no consistent hypnotizability-related modulation of heart rate and heart rate variability has been observed during suggestions for analgesia [21,38,47,66].

A mechanism triggered by physical interventions and able to reduce pain in healthy participants is the Diffuse Noxious Inhibitory Control (DNIC) originally described in animal models [27,28] and also defined "heterotopic counter-irritation" or "conditioned analgesia" [61]. It is elicited by the activation of the wide dynamic range (WDR) neurons of the spinal cord by nociceptive stimulation of one part of the body (conditioning stimulus). These neurons project to the subnucleus reticularis dorsalis of the medulla which, in turn, is involved in diffuse descending inhibition of spinal nociceptive neurons. As a consequence, a nociceptive stimulation (conditioned stimulus) applied after the beginning of a tonic conditioning stimulus is perceived as less painful than it was when applied alone. In humans, more than one component could influence the activation of DNIC and interact with it in pain control [19]; in fact, the placebo manipulation of the conditioning stimulus reduces its analgesic effect on the conditioned nociceptive stimulus, suggesting that neural circuits sustaining cognitive/emotional states may cooperate with the spino-bulbo-spinal circuit in determining analgesia [35,44,56]. Imaging studies support this view by demonstrating the contribution of higher-order brain regions such as the anterior cingulate cortex to DNIC [52]. In contrast to the explicit suggestions of analgesia, which are successfully used in the treatment of chronic pain, DNIC is impaired in a few chronic pain patients [2,36,39]. In fact, its efficacy characterizes various pain syndromes and predicts pain development and the response to treatment in patients [61].

There is only one report on DNIC as a function of hypnotisability [45]. In that study, cold-pressor test (CPT) was the conditioning stimulus; DNIC effects on pain perception and on the flexor reflex amplitude were investigated in participants with high (highs) and low hypnotizability scores (lows) before and after hypnotic induction. Since in both instances reduction of pain and of the reflex amplitude was observed only in highs, it was suggested that hypnotizability may be relevant to DNIC. In contrast to the suggestions for analgesia, no study has been conducted on the autonomic correlates of the activation of DNIC in healthy subjects.

The aim of the present study was to compare the effects of explicit suggestions of analgesia administered in the ordinary state of consciousness and of DNIC activation on pain perception and on heart rate in highs, lows and participants with intermediate scores of hypnotizability (mediums), who represent the largest part of the population [1,9,14].

2. Methods

2.1. Subjects

Participants were 137 healthy volunteers of both genders (age 20–27) recruited among Pisa University students who signed an informed consent. They were considered healthy on the basis of accurate anamnesis and enrolled if drug free for at least 2 weeks before the study. None of them reported cardiovascular risk factors (systemic hypertension, diabetes mellitus, smoking, hypercholesterolemia). Hypnotizability was assessed through the Italian version of the Stanford Hypnotic Susceptibility Scale (SHSS), form A [60] in order to recruit 20 consecutive highs (SHSS score ≥ 8/12), 20 lows (SHSS, A score ≤ 4/12) and 20 mediums (SHSS score = 5–7) who were informed that no further hypnotic induction will be performed in the successive 2 experimental sessions, scheduled at least 1 month after hypnotic assessment. On the day of the first experimental session, 9 subjects were excluded owing to their poor ability in determining the electrical threshold and/or evaluate the perceived pain. Thus, the studied persons ($N = 51$) were 18 highs (11 females), 18 lows (7 females,) and 15 mediums (10 females). The study was conducted according to the Declaration of Helsinki. The participants' privacy was observed.

2.2. Experimental procedure

All experimental sessions (Fig. 1A) were scheduled between 9 a.m. and 12 a.m., at least 2 h after the latest light meal and 6 h after the latest caffeine containing beverages. Immediately before sessions participants completed the State Anxiety Inventory (STAI-Y1) [51] to assess their emotional state and to study its influence on pain reports and heart rate. All participants had normal resting electrocardiogram (ECG) and blood pressure.

During sessions they were comfortably seated in an arm-chair in a semi-darkened, sound attenuated, temperature controlled room (20°–22°) and asked to maintain their eyes closed. They were submitted to a REAL and a SHAM session pseudo-randomly administered in each hypnotizability group. Both sessions consisted of 3 conditions of electrical nociceptive stimulations (Fig. 1B) of the left hand (2 min) alternated with resting conditions (4 min) (Fig. 1C). Three out of 51 subjects did not participate in the scheduled SHAM session owing to unexpected academic duties.

As shown in Fig. 1, sessions started with (1) the assessment of the stimulus intensity which could be detected at least twice out of 3 administrations, in order to test the excitability of the sensory system (innocuous test stimulus), and (2) the identification of the intensity of the nociceptive stimulus able to elicit a pain sensation scored 6 in a range from 0 (no pain) to 10 (maximum bearable pain). In both instances an isolated, constant-current stimulator (Digitimer, model DS7A) delivered 0.5 s duration stimuli to the left hand. Nociceptive thresholds were not studied to shorten the duration of stimulation conditions as much as possible (particularly the immersion in cold water) and to avoid central sensitization.

In the REAL session (Fig. 1B) nociceptive stimulation was administered: 1) in the absence of other concomitant stimuli (Control); 2) 30 s after starting the administration of explicit suggestions for glove analgesia (SUGG) [21] which lasted for the entire condition (2 min); 3) 30 s after the immersion of the right hand in cold water ($t = 10°$–12 °C, no circulating pump) aimed at activating the diffuse noxious inhibitory control (DNIC, 2 min) [12,30]. Suggestions for glove analgesia were administered in Italian and consisted of the explicit request to imagine to have the left hand protected against any possible pain ("*… you cannot feel pain because the thick glove you are wearing prevents you from feeling it … the glove's fabric is thick… you are not disturbed by the electrical stimulation at all… the glove protects you…*"). At the end of the SUGG condition, suggestion induced analgesia was reversed by specific instructions ("*…now your left hand is completely normal, you can feel everything…*").

In the SHAM session (Fig. 1B) the water temperature in DNIC was 30° instead of 10°–12 °C and in SUGG the instruction for glove analgesia was substituted by weather forecast information of the same duration (*please listen to me… Italian weather forecast have become reliable… I learned that next days will be stable…no rain…no wind…temperature will be fine… Italian families are very interested to weather forecast for the weekend … they rely on the provided information…*). After each nociceptive stimulus ($N = 3$), subjects had to score the perceived pain (Fig. 1B) in a scale from 0 (no pain) to 10 (unbearable pain).

In all sessions SUGG preceded DNIC because the activation of the Diffuse Noxious Inhibitory Control can outlast the immersion duration and the successive resting condition [29], whereas the effects of suggestions can be quickly reversed by specific instructions.

2.3. Signals recording and acquisition

ECG was recorded through 3 M Red Dot Ag/AgCl disposable electrodes placed according to the standard first ECG lead (DI). Signals were amplified by a LACE-Elettronica System amplifier (Pisa, Italy)

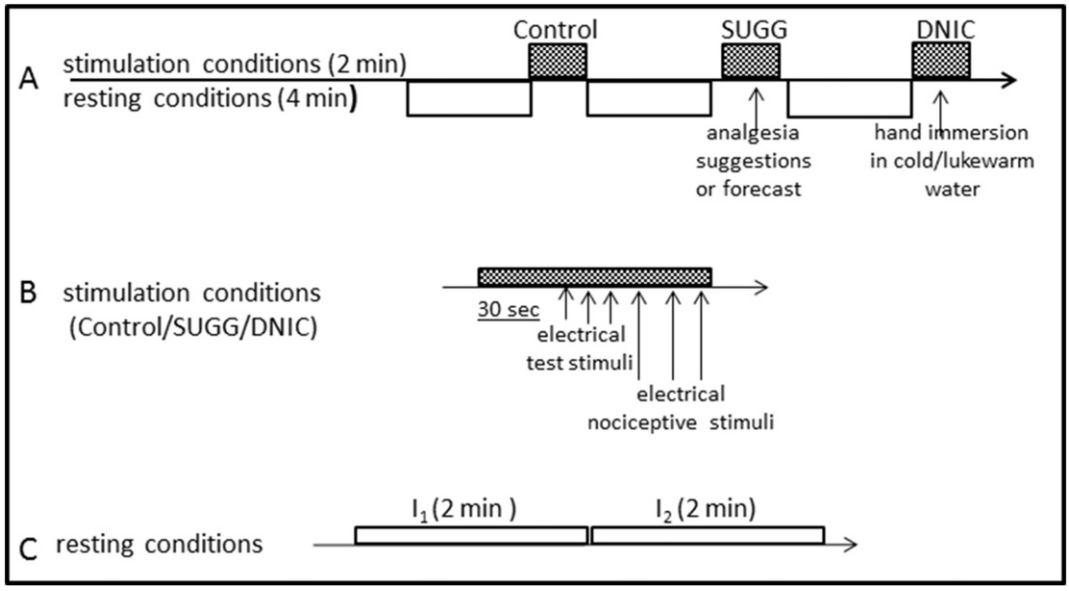

Fig. 1. Experimental procedure. Both REAL and SHAM sessions (A) started with the assessment of test and nociceptive stimuli (not illustrated). B illustrates the electrical stimulation procedure in Control, SUGG, and DNIC. C represents resting conditions.

and acquired by a National Instruments A/D Converter (sampling rate = 1 kHz) through a Labview software prepared ad hoc. ECG pre-processing involved baseline wander removing by linear filtering and stimulus induced artefactual wave cancelling by Singular Value Decomposition. On pre-processed ECG records, QRS detection was performed according to earlier studies recommendations [18,53]. In stimulation conditions the series of consecutive RR distances (RR = 1 / heart rate, ms) was used to characterize the prompt RR change occurring soon after the nociceptive stimulus by evaluation of the RR Turbulence [3–5,49]. The latter is a stimulus-locked variable defined by the Turbulence Onset (TO), which indicates the largeness of change occurring in the earliest 2 RR intervals after stimulation with respect to the latest two RR immediately before it, and by the Turbulence Slope (TS) which represents the slope of the RR recovery curve observed over the earliest 5 post stimulus RR intervals (for details, see [48]). Spectral analysis of ECG [54] could not be performed in stimulation conditions because they were not stationary; it was applied to resting conditions in order to assess the individual basal autonomic balance and exclude possible bias in the effects of nociceptive stimuli on the RR series.

The pneumogram was recorded through an inductive transducer (CompuMedics Life Systems, Victoria, Australia) wrapped around the chest at the level of the 10th rib. Respiratory cycles were detected and their frequency (RF, breath/min) was obtained by averaging on 2 min intervals. The Respiratory Frequency (RF) extracted from the pneumogram was computed only over resting conditions because the short intervals separating nociceptive stimuli prevented the reliable detection of stimulus-locked changes in the respiratory cycle.

2.4. Variables and statistical analysis

STAI scores reported before the REAL and SHAM sessions were analysed through repeated measures ANOVA (SPSS.15) following a 3 Hypnotizability (highs, mediums, lows) × 2 Gender (females, males) × 2 Session (REAL, SHAM) design.

2.4.1. Stimulation conditions

The intensity of the innocuous test stimulus and of the nociceptive stimulus, and pain scores (averaged over the 3 nociceptive stimulation of each stimulation condition) were submitted to repeated measures ANOVA according to a 3 Hypnotizability (highs, mediums, lows) × 2 Gender (females, males) × 2 Session (REAL, SHAM) × 3 Condition (Control, SUGG, DNIC) design. Since according to Cochrane criteria [20] pain reduction is considered clinically significant if it is larger than 30% of the initially reported pain, for each session the mean pain scores of SUGG and DNIC were expressed as percentages of the Control pain score and analysed through a 3 Hypnotizability × 2 Gender × 2 Session × 2 Condition (SUGG, DNIC) design.

The number of perceived test stimuli was analysed through non-parametric statistics (χ^2 between hypnotizability groups; Wilcoxon test between Conditions and Sessions).

Stimulus locked TO and TS (indices of the RR series Turbulence induced by the nociceptive stimuli) were analysed through repeated measures ANOVA according to a 3 Hypnotizability × 2 Gender × 2 Session × 3 Condition (Control, SUGG, DNIC) design.

After Bonferroni correction, the level of significance for subjective reports (innocuous and nociceptive stimulation intensities, number of detected test stimuli, pain reports) and turbulence variables (TO, TS) was set at $p = 0.008$.

2.4.2. Resting conditions

Analysis of RF, RR, SD and LF/HF as a measure of spectral heart rate variability (HRV) (Fig. 1C) was performed in order to ascertain whether participants exhibited similar autonomic balance before stimulation. Each resting condition (pre-Control, pre-SUGG, pre-DNIC) was divided in 2 Intervals (I_1, I_2). I_2 immediately preceded and I_1 immediately followed stimulation conditions. RR, RR Standard Deviation (SD) and LF/HF ratio were analysed through repeated measures ANOVA. Hypnotizability and Gender were *between* subjects factors. Session (REAL, SHAM), Times (pre-Control I_2, pre-DNIC I_2, pre-SUGG I_2) were *within* subjects factors. Since a few files were lost during acquisition, the degrees of freedom of the comparisons concerning RR, SD, LF/HF and RF do not correspond to those reported for the analysis of self reports. After Bonferroni correction, the level of significance was set at $p = 0.012$.

For all ANOVAs (stimulation and resting conditions), the Geenhouse-Geisser ε correction was adopted when necessary. Contrast analysis between conditions and unpaired *t*-tests between hypnotizability groups were performed.

3. Results

STAI scores differed significantly $F(1,45) = 107.24$, $p < 0.0001$, $\eta^2 = 0.719$) between the first (mean, SD; score = 40 ± 3.70) and second session (score = 45.66 ± 3.96), be it REAL or SHAM. However, they were in the normal range on both occasions and did not correlate with the intensity of the innocuous and nociceptive stimuli, pain reports, number of detected test stimuli, TO ad TS in any session and condition.

3.1. Stimulation conditions

3.1.1. Intensity of nociceptive stimuli

The intensity of the nociceptive stimuli able to elicit a pain intensity reported as 6 out of 10 in the Control condition was similar in all hypnotizability and gender groups and did not differ between the REAL (mean ± SD (mA); highs, 22.7 ± 10.76; mediums, 16.43 ± 6.87; lows, 16.65 ± 13.99; females, 2.15 ± 18.65; males, 17.82 ± 10.77) and SHAM session (highs, 19.71 ± 12.78; mediums, 13.14 ± 9.65; lows, 19.12 ± 11.33; female, 18.23 ± 8.99; males (16.82 ± 13.5).

3.1.2. Pain reports

Pain intensity reports exhibited significant Session ($F(1,42) = 17.002$, $p < 0.0001$, $\eta^2 = 0.396$) and Condition ($4,84) = 78.020$, $p < 0.0001$, $\eta^2 = 0.656$) effects. Decomposition of the significant Session × Condition interaction ($F(2,84) = 6.772$, $p < 0.001$, $\eta^2 = 0.570$) revealed that in both sessions pain decreased during DNIC (REAL: $t(1,50) = 99.944$, $p < 0.0001$; SHAM: $F(1,47) = 53.968$, $p < 0.002$) and SUGG (REAL: $t(1,50) = 103.482$; SHAM: $t(1,47) = 36.738$, $p < 0.0001$) with respect to the Control condition. Only during SUGG pain was lower in the REAL than in the SHAM session ($t(1,47) = 3.981$, $p < 0.0001$), whereas Control conditions did not differ between sessions.

ANOVA revealed also a significant Hypnotizability × Condition interaction ($F(4,84) = 4.821$, $p < 0.002$, $\eta^2 = 0.190$). Its decomposition (Table 1) showed that all participants reported lower pain in SUGG and DNIC than in Control (Fig. 2) and that highs perceived lower pain than lows in SUGG but not in DNIC independently of sessions (REAL or SHAM).

Mean values and Standard Deviation (SD) of pain reports are shown in Table A of the Supplementary Electronic Material.

When the pain scores reported for SUGG and DNIC were expressed as percentages of Control values (Table 2), significant Hypnotizability ($F(2,40) = 7.274$, $p < 0.002$, $\eta^2 = 0.267$) and Session effects ($F(1,40) = 16.096$, $p < 0.0001$, $\eta^2 = 0.287$) were found (Fig. 3A).

The former (Fig. 3A) revealed similar pain reduction in highs (who exhibited a pain reduction larger than 30%) and mediums (who exhibited a mean reduction of about 30%), larger pain reduction in highs than in lows ($F(1,30) = 15.033$, $p < 0.001$), no significant difference between mediums and lows (who exhibited a pain reduction always lower than 30%). The significant Session effect (Fig. 3B), consisting of larger pain decrease in the REAL than in the SHAM session in all participants, is represented in Fig. 3B.

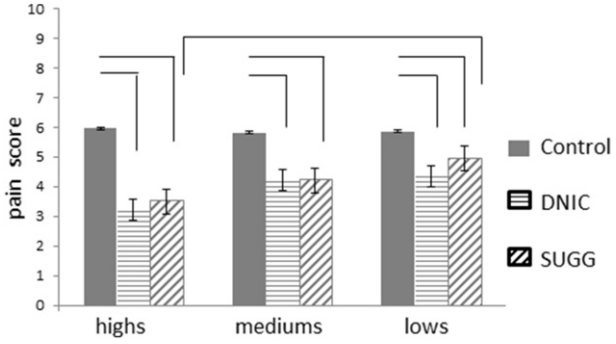

Fig. 2. Pain reports. Pain intensity scores (mean, SE). Lines indicate significant differences between stimulation conditions (Control, SUGG, DNIC) in each hypnotizability group (highs, mediums, lows). Lines indicate significant differences between groups in each condition and between conditions within each group.

It may be interesting to notice that the more sensitive within Hypnotizability analysis revealed a significant Session effect only in mediums ($F(1,13) = 11.226$, $p < 0.005$, $\eta^2 = 0.463$).

3.1.3. Intensity of the innocuous test stimulus

ANOVA did not reveal significant differences according to Session, Hypnotizability (mean ± SD, mA); REAL: highs, 2.42 ± 0.97; mediums, 1.94 ± 1.42; lows, 2.75 ± 0.69; SHAM: highs, 2.03 ± 0.60; mediums, 3.27 ± 4.18; lows, 2.42 ± 0.88) and Gender (REAL: females, 2.82 ± 1.25; males, 2.55 ± 0.76; SHAM: females, 2.74 ± 3.21; males, 2.55 ± 2.42).

3.1.4. Number of detected test stimuli

Non-parametric statistics did not show significant differences among hypnotizability groups (mean ± SD; highs, 1.8 ± 1.7; mediums, 1.94 ± 1.6; lows, 2.31 ± 1.4) and between Sessions (mean ± SD; REAL: 2.69 ± 1.05; SHAM: 2.56 ± 2.42). In contrast a significantly lower number of stimuli was detected in both Sessions during DNIC (REAL, $Z = 4.545$, $p < 0.0001$; SHAM, $Z = 4.926$, $p < 0.0001$) and SUGG (REAL, $Z = 3.364$, $p < 0.001$; SHAM, $Z = 3.963$, $p < 0.0001$). Mean values and SD are reported in Table B of Supplementary Electronic Material.

3.1.5. RR Turbulence

Despite the TO values suggesting lower Turbulence Onset in the REAL session and also some hypnotisability-related difference (Fig. 4), after Bonferroni correction Turbulence Onset did not exhibit any significant difference of Session, Hypnotizability, Gender and Condition. Low effect size (Session, $\eta^2 = 0.094$; Condition, $\eta^2 = 0.040$; Hypnotizability, $\eta^2 = 0.014$; Gender, $\eta^2 = 0.073$), however, prevents to exclude that significant differences may appear in larger samples.

Turbulence Slope values did not show any significant difference (Session, $\eta^2 = 0.007$; Condition, $\eta^2 = 0.001$; Hypnotizability, $\eta^2 = 0.046$; Gender, $\eta^2 = 0.0001$). Mean values and SD are reported in Table B (Supplementary Electronic Material).

Table 1
Pain scores: decomposition of the significant Hypnotizability × Condition interaction.

Highs	*Mediums*	*Lows*	Control	DNIC	SUGG
CONTROL > SUGG $F(1,17) = 78.046$, $p < 0.0001$	CONTROL > SUGG $F(1,14) = 20.704$, $p < 0.001$	CONTROL > SUGG $F(1,17) = 44.976$, $p < 0.0001$	ns	*Highs = lows*[a]	Highs < lows $t(1,34) = 3.069$, $p < 0.004$
CONTROL > DNIC $F(1,17) = 65.784$, $p < 0.0001$	CONTROL > DNIC $F(1,14) = 25.808$, $p < 0.0001$	CONTROL > DNIC $F(1,17) = 24.089$, $p < 0.0001$		*Highs = mediums*	*Highs = mediums*
DNIC = SUGG	DNIC = SUGG	SUGG = DNIC		*Mediums = lows*	*Mediums = lows*

[a] This comparison did not survive to Bonferroni correction but was borderline significant ($p < 0.009$).

Table 2
Pain changes during DNIC and SUGG.

Condition	Hypn	Session	REAL		SHAM	
		Gender	Mean	SD	Mean	SD
DNIC	Highs	f	0.53	0.27	0.49	0.33
		m	0.48	0.25	0.67	0.12
		Total	0.51	0.25	0.57	0.27
	Mediums	f	0.69	0.35	0.75	0.23
		m	0.57	0.24	0.84	0.24
		Total	0.65	0.31	0.78	0.23
	Lows	f	0.68	0.16	0.86	0.16
		m	0.74	0.21	0.82	0.17
		Total	0.71	0.19	0.84	0.16
SUGG	Highs	f	0.54	0.26	0.57	0.26
		m	0.52	0.27	0.82	0.17
		Total	0.53	0.26	0.68	0.25
	Mediums	f	0.50	0.29	0.79	0.26
		m	0.65	0.22	0.92	0.21
		Total	0.55	0.27	0.84	0.24
	Lows	f	0.90	0.23	0.88	0.26
		m	0.72	0.24	0.81	0.19
		Total	0.79	0.25	0.83	0.22

Note. Pain scores expressed as percentages of Control values.

3.2. Basal conditions

Mean RR in I_2 (2 min interval immediately preceding each stimulation condition) exhibited a significant Condition effect ($F(2,32) = 14.85$, $p < 0.0001$, $\eta^2 = 0.317$) sustained by lower pre-Control than pre-DNIC ($F(1,32) = 12.07$, $p < 0.001$) and pre-SUGG RR values ($F(1,32) = 22.88$, $p < 0.0001$). A significant Condition × Gender interaction ($F(2,62) = 8.16$, $p < 0.001$, $\eta^2 = 0.208$) was found for LF/HF; nonetheless, its decomposition did not reveal significant Gender and Condition differences. No significant difference was observed for the RR overall variability (SD) and for Respiratory Frequency. Mean values of all variables are reported in Tables C and D (Supplementary Electronic Material).

4. Discussion

The present study compares, for the first time, the analgesic effects due to the activation of the Diffuse Noxious Inhibitory Control with those induced by the administration of explicit suggestions of analgesia in healthy subjects with different levels of hypnotizability in their ordinary state of consciousness.

Findings show that both interventions reduce pain in all subjects, which may account for the ability to accept suggestions for analgesia observed in chronic pain patients almost independently of their hypnotizability score [8,23]. More importantly, when the pain scores reported during suggestions and DNIC are expressed as percentages of the Control condition (pain reduction), as suggested by Cochrane criteria [20], pain reduction is found larger in highs than in lows whereas mediums report intermediate pain scores independently of the specific pain manipulation which appears less relevant than hypnotizability.

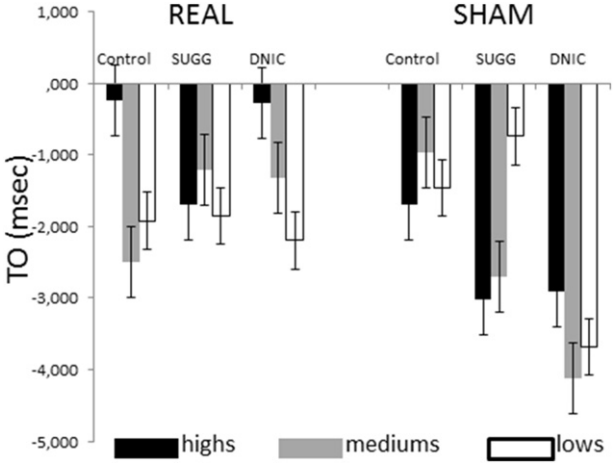

Fig. 4. RR turbulence onset (TO). TO (mean, SE) in highs (black bars), mediums (grey bars) and lows (white bars) in Control, SUGG and DNIC conditions.

The larger pain reduction induced by suggestions in highs with respect to lows was expected on the basis of several earlier findings [21,38,47,66]. Nonetheless, since mediums report mean pain reduction of about 30% and they represent the largest part of the general population [1,9,14], our findings show that, during experimental acute pain, analgesia can be obtained through both manipulation in approximately 85% of the healthy population.

The similar pain reduction induced by suggestions and DNIC implies that not only suggestions but also DNIC is more efficacious in highs than in lows. This replicates the findings of Sandrini et al. [45] supporting the idea that the Diffuse Noxious Inhibitory Control may exert its action through both sensory and cognitive mechanisms [19,35,52].

Present findings do not allow to identify the mechanisms sustaining the larger pain reduction occurring in highs with respect to lows after activation of the Diffuse Noxious Inhibitory Control. We hypothesize that the opioid contribution classically associated with DNIC induced analgesia is negligible in highs owing to their opioid μ_1 receptors low sensitivity. More relevant opioid contribution based on higher μ_1 sensitivity is possible in mediums and, even more, in lows [40] who exhibit the maximum μ_1 sensitivity together with the lowest ability to accept suggestions. Importantly, since high DNIC efficacy predicts lower

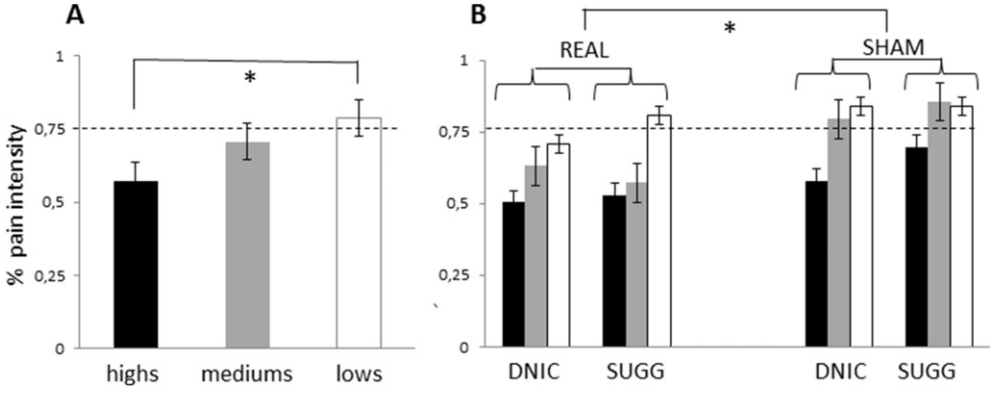

Fig. 3. Pain decrease during suggestions and DNIC. Pain intensity reported in DNIC and SUGG is expressed as a percentage of Control value. A) Hypnotizability effect; B) session effect. Lines with stars indicate significant differences. Dotted lines represent the level of pain decrease considered clinically relevant according to Cochrane criteria (www.cochrane.org/training/cochrane-handbook).

probability to develop post-surgical and successive persistent pain [62], it can be hypothesized that highs are less vulnerable than the general population to these side effects of surgical interventions.

Although the absence of autonomic modulation consistent with pain modulation agrees with earlier reports [21,38,47,66]and with the observation that pain-related perception, sensory-motor and autonomic control are separately controlled [43], the absence of significant differences in the stimulus-locked heart rate changes (turbulence) observed in the present study between Control conditions and DNIC/suggestions should be further investigated. It could be due to the short duration of the nociceptive stimulation as well as to the site of electrical stimulation which may be experienced as scarcely relevant. In fact, electrical nociceptive stimulation administered to the supraorbital nerve and eliciting blink reflex induced heart rate turbulence modulated by hypnotizability [48].

Our findings have not been biased by anxiety because STAI scores were always in the normality range [51] and did not correlate with any of the studied variables, despite the higher STAI scores reported on the day of the second session with respect to the first one (be it REAL or SHAM) suggesting that, independently of their sequence, the first session negatively primed the participants' experience.

Pain reports have not been biased by non-specific changes in sensory perception as the number of perceived test stimuli did not differ significantly between highs, mediums and lows, in contrast to pain reports, as well as between Sessions. The reduction in perceived test stimuli during DNIC and SUGG could be due to cross-modal distraction elicited by the concomitant stimuli, that is, the voice of the experimenter (SUGG) and the hand immersion (DNIC) in lukewarm water [10,33,34,57].

Although participants reported larger pain reduction in the REAL than in the SHAM session, pain reduction was found also in the SHAM session. We may hypothesize that the weather forecast information administered may have acted through distraction [6,7,11,17,37] and that also the non-noxious water temperature may have triggered the Diffuse Noxious Inhibitory Control mechanism, although to lower extent [58].

Finally, the resting heart and respiratory activities (which were similar in highs, mediums and lows) cannot have biased the heart rate Turbulence observed in stimulation conditions and cannot have buffered possible Turbulence differences between stimulation conditions as they were similar in pre-SUGG and pre-DNIC resting intervals. The slightly longer RR interval observed in all participants in resting pre-DNIC and pre-SUGG intervals with respect to pre-Control could be attributed to familiarization with electrical stimulation.

Findings should be confirmed in a larger sample because of the low effect size observed in the present study for a few comparisons. After our exploratory investigation, larger samples are required also because subtypes of highs have been described [55] and mediums represent a population even more heterogeneous than highs owing to the method of hypnotic assessment. In fact, hypnotizability scales may provide the same score of hypnotizability in individuals who may have passed very different items. In addition, the covariance of traits potentially able to influence pain perception should be studied ([41,67]. Finally, it should be remarked that findings cannot be extended to pain patients in the absence of controlled clinical trials.

In conclusion, the present study shows that high hypnotizability is a favourable condition for pain control through both suggestions of analgesia and activation of the Diffuse Noxious Inhibitory Control.

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