Effects of specific hypnotic suggestions on mechanical and thermal sensitivity of healthy volunteers: randomized and double-blind study

Efeito de sugestões hipnóticas específicas sobre a nocicepção mecânica e térmica em voluntários saudáveis: estudo randomizado e duplo-cego

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ABSTRACT

BACKGROUND AND OBJECTIVES: Hypnotic suggestions for hypoalgesia or analgesia are efficient for relieving different pain conditions, presenting few or no side effects. However, little is known about its direct effect on the modulation of peripheral nociception. The goal of this study was to evaluate the mechanical and thermal response after specific hypnotic suggestions in healthy volunteers.

METHODS: This is a randomized double-blinded controlled trial that aimed to evaluate both mechanical and thermal nociception after specific hypnotic suggestions in healthy volunteers. For this, twenty-seven participants were enrolled, according to the following eligibility criteria: age between 18-65 years and absence of pain complaints or psychological disorders. After signed Free Informed Consent Term (FICT) the participants were divided by a computer-generated randomization in three groups: sham group (no induction of hypnosis), hypnosis-induced pain group and hypnosis-induced analgesia group. Susceptibility to hypnosis was assessed through the Waterloo-Stanford Group C (WSGC) scale of hypnotic susceptibility and outcomes included evaluation of questionnaires (Hospital Anxiety and Depression Scale and Short Form Brief Pain Inventory) as well as the examination of mechanical and thermal nociception through the Quantitative Sensory Testing (QST), a tool widely used to investigate somatosensory sensitivity by assessing functions of small A-δ and C nerve sensory fibers, before and after specific hypnotic suggestion for pain and analgesia made by a qualified hypnotherapist.

RESULTS: Data demonstrated that specific hypnotic suggestions induced significant changes in mechanical and thermal sensitivity. The pain group revealed an increase in mechanical hyperalgesia and allodynia, while the analgesia group increased pain thresholds to thermal stimulations, being conditioned to withstand temperature changes after hypnosis, demonstrating a modulatory effect for both pain and analgesia sensations in healthy volunteers.

CONCLUSION: The evidence presented in this study supports the use of the hypnosis technique as an auxiliary tool in clinical practice.

Keywords: Analgesia, Hypnosis, Pain, Quantitative sensory test.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Sugestões hipnóticas de hipoalgesia ou analgesia são eficientes para aliviar diferentes quadros álgicos, apresentando poucos ou nenhum efeito colateral. No entanto, pouco se sabe sobre seu efeito direto na modulação da nocicepção periférica. O objetivo deste estudo foi avaliar a resposta mecânica e térmica após sugestões hipnóticas específicas em voluntários saudáveis.

MÉTODOS: Este é um estudo randomizado e duplo-cego que visou avaliar a nocicepção mecânica e térmica após sugestões hipnóticas específicas em voluntários saudáveis. Para isso, vinte e sete participantes foram selecionados, de acordo com os seguintes critérios de elegibilidade: idade entre 18-65 anos e ausência de distúrbios psicológicos e de queixas de dor. Após a assinatura do Termo de Consentimento Livre e Esclarecido (TCLE), os participantes foram divididos por randomização gerada por computador em três grupos: grupo sham (sem indução de hipnose), grupo dor induzida por hipnose e grupo analgesia induzida por hipnose. A suscetibilidade à hipnose foi avaliada através da escala

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HIGHLIGHTS
- Specific hypnotic suggestions can modulate peripheral nociception in healthy subjects.
- Data show a modulatory effect for both pain and analgesia sensations.
- Hypnosis can be considered a feasible technique for the clinical pain management.

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Waterloo-Stanford Group C (WSGC) de suscetibilidade hipnótica e os resultados incluíram a avaliação de questionários (Escala Hospitalar de Ansiedade e Depressão e Inventário Breve de Dor), bem como o exame de nocicepção mecânica e térmica através do Teste Sensorial Quantitativo (QST), uma ferramenta amplamente utilizada para investigar a sensibilidade somatossensorial por meio da avaliação das funções das fibras sensoriais finas dos nervos A-δ e C, antes e após sugestão hipnótica específica para dor e analgesia aplicada por um hipnoterapeuta qualificado.
RESULTADOS: Os dados mostraram que as sugestões hipnóticas específicas induziram mudanças significativas na sensibilidade mecânica e térmica dos indivíduos. O grupo dor revelou aumento da hiperalgesia mecânica e da alodinia, enquanto o grupo analgesia aumentou os limiares de dor por estímulos térmicos, sendo condicionado a suportar mudanças de temperatura após a hipnose, demonstrando efeito modulador tanto para as sensações de dor quanto de analgesia em voluntários saudáveis.
CONCLUSÃO: As evidências apresentadas neste estudo sustentam o uso da técnica de hipnose como ferramenta auxiliar na prática clínica.
Descritores: Analgesia, Dor, Hipnose, Teste quantitativo sensorial.

INTRODUCTION

Hypnosis is considered a psychological intervention indicated to treat diseases such as depression, obesity, and phobias, and is one of the oldest forms for pain management[1]. Non-pharmacological nature, convenience of delivering treatment, and few side effects are major advantages of this therapy[2]. It can be delivered in a pre-recorded format in the presence of a hypnotherapist. Despite much evidence of its efficacy in chronic and acute pain therapy, little is known about its direct effect on the modulation of nociception[3-7].
There are different approaches to delivering hypnosis therapy. Many applications involve minimal induction with suggestions for relaxation and the use of imagery, that is often referred to as "neutral hypnosis"[2,8,9]. In other cases, a specifically focused analgesia suggestion is employed, aiming to alter perceptual experience and behavior[2]. Some studies have shown that hypnotic relaxation is equally effective as an analgesic suggestion, while others have indicated that specific analgesic cues are more effective[6,10-12]. Nonetheless, the analgesic effect of hypnosis can be so powerful that surgical procedures have even been performed without anesthesia[13]. In fact, several studies support hypnosis as a potential approach to relieve unaddressed pain and anxiety in burn patients undergoing wound care, managing labor pain, and fibromyalgia[4,14,15].
Not all human beings respond equally to hypnotic intervention. Hypnotic susceptibility determines direct analgesic efficacy that is critical to the treatment success[6]. Susceptibility scoring is described as the aggregation of behavioral responses to a series of individual suggestions[6]. Several scales have been generated such as German Norms for Harvard Group Scale of Hypnotic Susceptibility (HGSHS)[16], Stanford Hypnotic Susceptibility Scale (SHSS), and a more recent Waterloo-Stanford Group C (WSGC)[17]. WSGC consists of hypnotic induction followed by the presentation of 12 hypnotic suggestions (hand lowering, arm rigidity, and immobilization, for example), which classifies individuals as low, medium, or high hypnotic susceptibility, describing not only their ability to enter a hypnotic state but also a correlation with their postural control[18]. Indeed, pain reduction was found to be more effective in individuals who were considered more susceptible (highly hypnotizable) to hypnosis, when hypnotic intervention was performed for analgesia[19,20].
To better understand the hypnotic analgesia, it is important to differentiate cognitive and behavioral elements from peripheral sensory perception[21]. Hence, this study examined the effects of specific hypnotic suggestionsin peripheral sensitivity in a healthy volunteer, with no current pain complaints.
The goal of this study was to evaluate the mechanical and thermal response after specific hypnotic suggestions in healthy volunteers.

METHODS

This is a randomized, double-blinded controlled clinical trial. The Consolidated Standards of Reporting Trials (CONSORT), CONSORT for Abstracts (CONSORT-A) and the Template for Intervention Description and Replication (TIDieR) checklist and guide were followed for the elaboration of this manuscript.
Twenty-seven volunteers were recruited from the population of healthy university students by advertisements posted in the university. The following inclusion criteria were applied: age between 18 and 65 years, and absence of complaints of pain or psychological disorders.
Subjects with a history of major psychiatric disease, substance abuse, or those unable to understand the consent form, individuals complaining of pain, and severe systemic, metabolic, or neurological disease capable of influencing the Quantitative Sensory Testing (QST) were excluded from this study. The protocol and informed consent forms were reviewed and approved by the local Ethics Committee on Human Research (CEPSH-ICB; CAAE: 87585918.2.0000.5467).
After all participants signed the Free and Informed Consent Term (FICT), a computer-generated randomization (Excel software) was used to assign participant to three different groups, this information was kept confidential in an opaque envelope. The groups were namely a) sham group (no induction of hypnosis), b) hypnosis-induced pain group, and c) hypnosis-induced analgesia group, for these two last groups hypnotic suggestion for pain and analgesia was given targeting the increase and decrease of the subject's pain and control over their sensations.
Following the initial procedures, the hypnotherapist was blinded to participant hypnosis susceptibility score, and the outcome assessor was blinded to group allocation. To objectively assess peripheral sensitization, questionnaires and Quantitative Sensory Testing (QST) were used. This analysis quantifies the peripheral pain sensitivity transmitted by thin (C) or thick sensory fibers (small A-δ) of the peripheral nervous system (PNS). This allows determination of basal and pain

thresholds to mechanical and thermal stimuli, in addition to enabling the detection of certain conditions, like hyperalgesia or hyperpathia[22,23]. All eligible volunteers received an explanation of the study objectives. All steps conducted in this study were represented in the figure 1 which contains a detailed explanation of the validated questionnaires applied to assess comorbidities and pain symptoms.

Questionnaires

In addition to standard demographic questions, the following questionnaires were used to assess comorbidities and pain symptoms: Alcohol Use Disorders Identification Test (AUDIT)[24], Hospital Anxiety and Depression Scale (HADS)[25] for anxiety and depression disorders, and Brief Pain Inventory – Short Form (BPI)[26] for somatosensory symptoms of pain. Details of these validated questionnaires used routinely are described in figure 1.

Hypnotic susceptibility

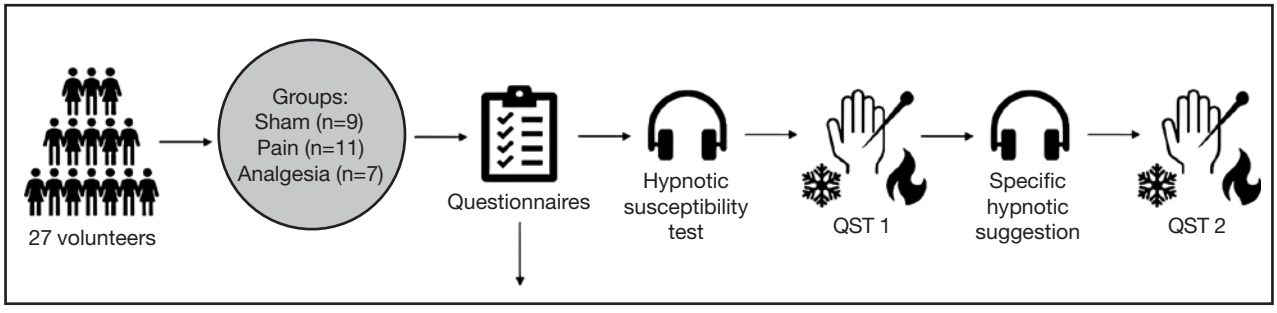
Waterloo-Stanford Group C Scale of Hypnotic Susceptibility (WSGC)[17] was used to determine the hypnotic susceptibility on a score from 0 to 12. Testing for hypnotic susceptibility was performed by a qualified hypnotherapist. The procedure was verbally standardized for all volunteers through a headphone containing four sensory families: psycho-imaginary, psycho-conflictive, polyvalent, and sensory. A sophisticated infrastructure was not required, only a quiet room with a comfortable chair.

After a hypnotic induction of about 20 minutes followed by the presentation of 12 hypnotic suggestions (1: Hand lowering; 2: Moving hands together; 3: Mosquito hallucination; 4: Taste hallucination; 5: arm rigidity; 6: dream about hypnosis; 7: arm immobilization; 8: age regression; 9: music hallucination - hear jingle bells; 10: negative visual hallucination; 11: posthypnotic suggestion - draw a doodle of a tree on the response booklet, and 12: posthypnotic amnesia), all volunteers undergone the hypnotic susceptibility scale to be classified as low (0-3 points), moderate (4-8 points), or high (9-12 points) susceptibility to hypnosis according to their score.

Specific hypnotic suggestions

Hypnosis was performed by a qualified hypnotherapist with 27 years working at the *Hospital das Clínicas* (Clinical Hospital) of the *Universidade de São Paulo* (USP - University of São Paulo), in face-to-face format. No participant had previous experience with hypnosis. A blinded assistant recorded all data. Hypnosis protocol consisted of two phases: induction and hypnotic suggestions. Hypnotic induction was standardized to be equally applied to all subjects, except to the sham group. The standard hypnotic protocol begins with an induction that was associated with breathing and relaxation, where subjects received suggestions to focus their attention on a single stimulus until reaching a trance state. This phase lasts around 10 minutes.

After the induction, the hypnotic suggestion phase started, working on the imaginary, giving color, size, and shape to the sensation referred according to the hypnotic suggestion for pain and analgesia was given targeting the increase and decrease of the subject's pain and controls over their sensations in those groups, rescuing and using an interpretation already known to the hyp-



SOCIODEMOGRAPHIC ASSESSMENT	Information about gender, age and skin color were collected according to The Brazilian Institute of Geography and Statistics (IBGE) criteria of 2010. Economic classification was made with Socioeconomic scale according to Brazilian Criteria of Economic Classification (BCEC) of the Brazilian Association of Populational Studies (ABEP) 2011.
ALCOHOL USE DISORDER IDENTIFICATION TEST (AUDIT)	Consists of 10 items, which covers the domains of alcohol consumption, drinking behavior, and alcohol related problem. Responses were scored from 0 to 4, giving a maximum possible score of 40. The cut--off points for non- hazardous consumption considered was ≤ 7.
HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)	Contains 14 items: 7 to evaluate anxiety and 7 to depression and has a cut-off point of ≥ 8 for anxiety and ≥ 9 for depression. Each of your items can be scored zero (0) to 3, composing a maximum score of 21 points for each scale.
BRIEF PAIN INVENTORY (BPI)	Consists of 9 items: used to evaluate the presence of pain and its intensity/severity, localization, and impact (interference of pain) in individual's lives in a scale 0 to 10. The cut-off point was ≤ 5 to be eligible for the study.

Figure 1. Flowchart of the study population and experiment design

notized person[27]. For example, as the area evaluated was the hand, in the pain group, the participant was asked to imagine the hand on fire, and the color and shape of the fire were asked, thus inducing an increase in sensitivity in that region.
In the analgesia group, the participant was asked to imagine or remember the sensation of sitting on the hand for a long period, causing tingling and numbness, inducing a loss of sensitivity in the area. The control group was undergone to the same procedures as other groups, but without induction or programming phase applied. They were asked to control breathing and relax. The experimental manipulations (induction + programming/suggestions) lasted for 20 min.

Quantitative Sensory Test (QST)
All QST were performed according to the study[28] at baseline and after hypnosis intervention on glabrous skin of the participant's left hand thenar eminence. During the test, participants were seated in a comfortable chair in a quiet room and kept their eyes closed during evaluations. All participants were subjected to a basal QST session (before hypnosis induction) and post-hypnotic intervention.
a) Mechanical detection and mechanical pain threshold: was measured using a standardized set of modified von Frey hairs that exert forces between 0.25 and 1079 mN (Somedic AB™, Horby, Sweden). The contact area of von Frey hairs with the skin (hand) had uniform size and shape (rounded tip, 0.5 mm in diameter) to avoid sharp edges that would facilitate nociceptor activation. The assessment started with the lowest filament. One affirmative answer meant perception of the filament. If the filament used was not felt, a filament with higher graduation would be used. The result was analyzed from the first filament perceived disregarding the filaments that were not perceived. Mechanical detection thresholds (MDT) and mechanical pain thresholds (MPT) were defined as the lowest pressure that generated a sensation of touch or pain, respectively. Mechanical pain sensitivity (MPS) was tested using the von Frey filament four times higher than that used for MPT, in addition, the pain intensity was also rated by a visual analog scale (VAS).
b) Dynamic allodynia: stimulus-response-functions for dynamic mechanical allodynia (DMA) were determined using a standardized brush (Somedic™, Sweden) exerting a force of 200–400 mN, applied only once. The subject was asked to provide a pain rating for each stimulus on a 0-100 mm numerical rating scale (NRS), with 0 indicating "no pain", and 100 indicating "most intense pain imaginable".
c) Wind-up ratio: the wind-up ratio is defined as the perceptual correlation of temporal pain summation for repetitive mechanical stimuli. In this test of temporal summation, the perceived magnitude of a single von Frey stimulus was compared to that of a train of 10 stimuli of the same force repeated at a 1/s rate (166 mN). The train of von Frey stimuli was given within a small area of 1 cm^2 and the subject was asked to provide a rating representing the pain by the end of the training using VAS. The mean pain rating of repeated over single stimuli was calculated as the wind-up ratio (WUR).
d) Thermal detection and thermal pain thresholds: tests for thermal sensation were performed based on a TSA 2001-II (MEDOC™, Israel) thermal sensory testing device. Cold detection threshold (CDT) and warm detection threshold (WDT) were measured first followed by heat pain threshold (HPT) and cold pain threshold (CPT), respectively, using the Method of Limits[29]. For the measurement of CDT and WDT, subjects received four successive ramps of gradually decreasing or increasing temperature, starting from a resting neutral temperature of 32°C, at a rate of 1°C per second[21,30]. Subjects were instructed to press a response button when a thermal sensation (either cold or warm) was first perceived. Pressing the button resulted in the automatic recording of the threshold temperature and returning of the thermode to the neutral temperature. Thermal ramps were repeated every 4-6s. A similar procedure was applied for determining CPT and HPT, but the stimuli were applied at 20 to 30 sec intervals, and the subjects were instructed to press the response button immediately after perceiving the thermal sensation as painful. Thermal thresholds were determined by averaging the reading of the four successive stimuli, discarding the reading most separated from the mean, and recalculating the average of the three remaining temperatures[31]. The intensity of pain evoked by suprathreshold stimuli was also assessed. For warm (WST) and cold (CST) suprathreshold, there was a constant increase (46°C and 48°C) or decrease (10°C and 5°C) from neutral temperature with a speed of 2°C/s, respectively. The means of the two VAS scores obtained during the suprathreshold stimuli were assessed.

Statistical analysis
Continuous quantitative variables were expressed as means, as standard error of the mean (SEM), or as standard deviation (SD), while nominal categorical variables were expressed in percentage (%). Data was assessed for normal distribution, failing which non-parametric tests were applied. Wilcoxon test assessed pre- and post-hypnosis of each group and the Kruskal-Wallis test was applied for statistical comparisons of the three groups. Data were analyzed on SPSS Statistics 20™ (IBM, Seattle, USA) and graphs were generated in GraphPad Prism™ (Version 8, GraphPad Software Inc., San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Epidemiological data of healthy individuals
Of the twenty-seven healthy participants, 10 men (37%; mean age: 35.50±5.195) and 17 women (63%; mean age: 36.82±3.536) were enrolled in this study (Figure 2A). According to the sociodemographic information, 74% (n= 20) of the participants self-declared as white, 18% (n= 5) as black, and the remaining 8% (n= 2) as Asian or aboriginal. Most of the participants (63%, n=19) were classified as class C (21.56±1.029) with an income corresponding to 4-10 minimum wages. Regarding alcohol abuse, the Alcohol Use Disorders Identification Test (AUDIT) demonstrated that 100%

A

CHARACTERISTIC	Gender	n	%
	Female	17	63
	Male	10	37
	Category	Mean	SEM
Alcohol abuse (AUDIT) Socioeconomic classification (ABEP) Hypnotic induction score	Age	36	± 2.88
	Low risk or abstention	2.67	± 0.49
	C1	21.56	± 1.029
	Moderate	6.16	± 0.34
Brief Pain Inventory (BPI)	Average pain	2.07	± 0.36
	Current pain	0.66	± 0.24
	Pain impact	1.00	± 0.30

B

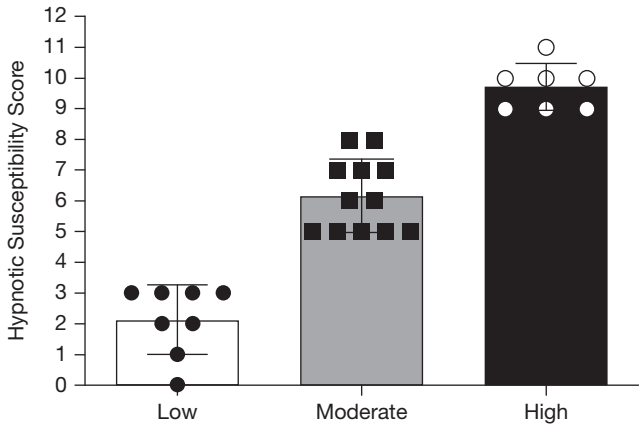


Figure 2. Epidemiological data and hypnotic susceptibility of healthy individuals

(n= 27) of the participants were at low alcoholism risk or abstaining (Figure 2A).

The presence of pain over the previous 24 hours was assessed by using Brief Pain Inventory (BPI), demonstrating the sensory dimension (average and current pain), and the impact of pain on quality of life (general activities) through the Visual Analog Scale (VAS). All individuals had a null or very low (less than 5) pain score (Figure 2A), making them eligible for the study. Still, when evaluated the hypnotic susceptibility scale most of the participants, 44% (n = 12), were classified as moderately susceptible (6.16±0.34) to hypnosis. The remaining part of the sample demonstrated high (9.71±0.28, 26%, n= 7)) or low (2.12±0.39, 30%, n= 8) susceptibility to hypnosis (Figure 2B). There were no differences among genders when evaluated.

General characteristics of volunteers were demonstrated as absolute numbers (n), percentages (%), mean and standard error of the mean (SEM) according to evaluation through validated questionnaires. (A) indicates the epidemiological data and (B) the hypnotic susceptibility of healthy subjects. All volunteers were submitted to the hypnotic susceptibility scale performed by a qualified hypnotherapist; the classification consists of low hypnotizability (0-3 points), moderate hypnotizability (4-8 points), or high hypnotizability (9-12 points). Neither the participants, the hypnotherapist nor the QST examiners were informed about the results of the susceptibility evaluation. GraphPad Prism 8.0.

Quality of life of individuals subjected to hypnosis procedure

The assessment of emotional aspects and related effects on the participant's quality of life using the HADS showed that 52% (n= 14) had symptoms of anxiety (n= 6), depression (n= 3) or both (n= 5) concomitantly (Table 1). Of these participants with emotional disturbances, most of them (50%, n= 7) were moderately susceptible to hypnosis.

Data correspond to the mean±sem of 27 patients expressed as a percentage (%) extracted from the Hospital Anxiety and Depression Scale (HADS) questionnaire.

Table 1. Assessment of the presence of anxiety and depression symptoms in healthy individuals undergoing hypnosis protocol

Emotional aspects	n	%	mean±sem
Absence	13	48	
Presence	14	52	
Anxiety	6	42.8	10.17±1.10
Depression	3	21.4	9.33±0.33
Both	5	35.5	

sem = standard error of the mean

Effect of specific hypnotic suggestion on peripheral sensitivity

Subjects were arranged in three different groups: sham (n=9), pain (n=11), and analgesia (n=7). Results of mechanical and thermal quantitative sensory testing are shown in tables 2 and 3, respectively.

The subjects were divided into sham (n= 9), pain (n=11), and analgesia (n=7) groups, and mechanical exteroceptive sensitivity were obtained through von Frey filaments measured in millinewtons (mN). The detection values for temperature were measured on hand, in celsius degrees (ºC). Visual Analogue Scale (VAS): 0 to 100 mm, was used for mechanical and thermal mensuration. Means and standard deviation (SD) of raw data were compared using a non-parametric Wilcoxon test for comparison before (Pre-hypnosis) and after (Post-hypnosis) hypnosis; p-value considered significant was <0.05.

Pain caused by mechanical hyperalgesia through repetitive painful stimulation was exacerbated by hypnosis in the pain group, once variation in pain intensity was positive after specific hypnotic suggestion (MPS, pre: 8.00±10.667/post: 15.27±12.900, p=0.011 – Table 2). In contrast, no significant result was observed in the analgesia group (MPS, pre: 9.42±12.67/post: 0.57±1.133, p=0.058 - Table 2). The analysis between groups showed no difference between analgesia and pain groups (p=0.0785 – Kruskal-Wallis test – Table 4).

Additionally, the pain group reported greater pain intensity in response to the brush touch (DMA, pre: 0.00±0.000/ post:

Table 2. Mechanical QST-parameters of healthy subjects

		SHAM		PAIN		ANALGESIA	
		Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis
MDT (mN)	mean±SD	0.42±0.261	0.88±1.171	0.434±0.258	0.44±0.355	0.89±1.074	25.086±62.456
	Negative Rank (mean)	0.00		2.75		2.00	
	Positive Rank (mean)	1.50		5.00		2.67	
	Wilcoxon p value (two-tailed)	0.180		0.916		0.273	
MPT (mN)	mean±SD	434.94±491.148	330.96±438.657	58.56±56.562	48.00±63.292	219.31±207.555	663.37±522.605
	Negative Rank (mean)	3.00		4.42		2.00	
	Positive Rank (mean)	1.00		4.75		3.80	
	Wilcoxon p value (two-tailed)	0.144		0.233		0.075	
MPS (VAS)	mean±SD	1.44±2.351	3.11±3.620	8.00±10.667	15.27±12.900	9.42±12.67	0.57±1.133
	Negative Rank (mean)	2.00		1.00		3.90	
	Positive Rank (mean)	4.25		5.50		1.50	
	Wilcoxon p value (two-tailed)	0.173		0.011		0.058	
DMA (VAS)	mean±SD	0.00±0.000	1.11±2.088	0.00±0.000	10.18±11.694	0.57±1.511	0.00±0.000
	Negative Rank (mean)	0.00		0.00		1.00	
	Positive Rank (mean)	2.00		4.50		0.00	
	Wilcoxon p value (two-tailed)	0.109		0.012		0.317	
WUR	mean±sd	0.294±0.492	0.652±1.655	1.06±1.406	1.38±0.864	2.652±1.650	0.00±0.000
	Negative Rank (mean)	1.50		5.00		3.50	
	Positive Rank (mean)	3.00		5.00		0.00	
	Wilcoxon p value (two-tailed)	>0.999		0.374		0.028	

SD = standard deviation; MDT = mechanical detection thresholds; MPT = mechanical pain thresholds; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; WUR = wind-up ratio; VAS = visual analog scale.

Table 3. Thermal QST-parameters of healthy subjects

		SHAM		Pain		Analgesia	
		Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis
CDT (ºC)	mean±sd	29.00±1.224	28.66±1.085	29.74±0.996	30.09±1.148	28.42±1.133	23.50±10.45
	Negative Rank (mean)	5.08		5.50		5.00	
	Positive Rank (mean)	4.83		5.50		1.50	
	Wilcoxon p value (two-tailed)	0.342		0.092		0.063	
WDT (ºC)	mean±sd	34.35±1.227	34.24±0.901	34.02±0.895	33.59±0.592	34.62±0.703	37.17±5.663
	Negative Rank (mean)	5.20		5.94		1.50	
	Positive Rank (mean)	4.75		3.75		4.50	
	Wilcoxon p value (two-tailed)	0.678		0.041		0.116	

Continue...

Table 3. Thermal QST-parameters of healthy subjects – continuation

		SHAM		Pain		Analgesia	
		Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis	Pre-Hypnosis	Post-Hypnosis
CPT (ºC)	mean±sd	11.96±9.564	13.34±8.228	12.58±10.583	23.08±7.243	18.28±8.290	14.31±10.310
	Negative Rank (mean)	3.50		3.00		4.42	
	Positive Rank (mean)	8.00		6.30		1.50	
	Wilcoxon p value (two-tailed)	0.859		0.008		0.034	
HPT (ºC)	mean±sd	42.00±6.111	44.94±3.470	44.59±3.898	39.21±4.428	41.51±3.456	45.48±3.251
	Negative Rank (mean)	5.00		6.50		0.00	
	Positive Rank (mean)	5.00		1.00		4.00	
	Wilcoxon p value (two-tailed)	0.374		0.004		0.018	
CST (VAS)	mean±sd	23.87±24.292	29.50±33.721	38.90±30.623	55.15±27.633	41.50±26.229	29.35±26.305
	Negative Rank (mean)	3.00		0.00		4.00	
	Positive Rank (mean)	5.40		5.00		0.00	
	Wilcoxon p value (two-tailed)	0.208		0.008		0.018	
WST (VAS)	mean±sd	20.62±22.108	24.56±28.708	38.65±30.862	54.00±27.575	45.64±26.087	31.07±26.168
	Negative Rank (mean)	3.33		2.00		4.00	
	Positive Rank (mean)	5.20		5.89		0.00	
	Wilcoxon p value (two-tailed)	0.263		0.009		0.018	

SD = standard deviation; CDT = cold detection threshold; WDT = warm detection threshold; CPT = cold pain threshold; HPT = hot pain threshold; CST = cold suprathreshold; WST = warm suprathreshold; VAS = visual analog scale

10.18±11.694, p=0.012 – Table 2). This was also observed comparing with the analgesia group (p=0.0029 – Kruskal-Wallis test, Table 4). In turn, the sham and analgesia groups reported an almost zero pain intensity in response to this stimulus, as expected considering the evaluation of healthy individuals. Regarding the wind-up ratio, statistical differences (p=0.028) were observed in the analgesia group (WUR, pre: 2.652±1.650/ post: 0.00±0.000- Table 2). After being subjected to hypnosis, the analgesia group presented statistical differences (p=0.0305) in relation to the pain group (Kruskal-Wallis test, Table 4).

Furthermore, differences in mechanical detection (MDT) and mechanical pain (MPT) thresholds were not observed intra-groups for any of them. However, when assessing the interaction between groups, a significant difference in the pain versus the analgesia group occurred in the MPT (p=0.0294– Kruskal-Wallis test, Table 4). Finally, regarding the mechanical exteroceptive sensitivity assessment, as expected, the sham group (no induction of hypnosis) showed no statistical difference after hypnosis for any of the assessed parameters, as shown in Table 2.

The measurement of exteroceptive thermal sensitivity demonstrated that the individuals presented normal range detection thresholds with no alteration after hypnosis in almost all groups, except for the pain group, which presented a significant difference for the warm detection threshold (WDT, pre: 34.02±0.895/post: 33.59±0.592, p=0.041 – Table 3) after specific hypnotic suggestion. In addition, a statistical difference was observed in relation to the analgesia group (p=0.0035– Kruskal-Wallis test, Table 4).

Table 4. Interaction of mechanical and thermal quantitative sensory testing parameters of healthy subjects between groups

Kruskal-Wallis test		MDT (mN)	MPT (mN)	MPS (VAS)	DMA (VAS)	WUR	CDT (ºC)	WDT (ºC)	CPT (ºC)	HPT (ºC)	CST (VAS)	WST (VAS)
Pre	Sham vs. Pain	>0.9999	>0.9999	>0.9999	0.0196	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999
	Sham vs. Analgesia	>0.9999	>0.9999	>0.9999	0.3738	0.0404	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999
	Analgesia vs. Pain	>0.9999	>0.9999	>0.9999	>0.9999	0.4595	0.6239	>0.9999	>0.9999	>0.9999	>0.9999	>0.9999
Post	Sham vs. Pain	>0.9999	0.6747	0.8458	>0.9999	0.2851	0.1552	>0.9999	0.1048	0.0542	0.3410	0.9327
	Sham vs. Analgesia	0.5142	>0.9999	>0.9999	0.0127	>0.9999	>0.9999	0.5769	>0.9999	>0.9999	>0.9999	>0.9999
	Analgesia vs. Pain	0.0842	0.0294	0.0785	0.0029	0.0305	0.0053	0.0035	0.4447	0.0613	>0.9999	0.9837

MDT = mechanical detection thresholds; MPT = mechanical pain thresholds; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; WUR = wind up ratio; CDT = cold detection threshold; WDT = warm detection threshold; CPT = cold pain threshold; HPT = hot pain threshold; CST = cold suprathreshold; WST = warm suprathreshold

The subjects were divided in sham (n= 9), pain (n=11) and analgesia (n=7) groups. Kruskal-Wallis test was performed for statistical comparisons of the three groups pre and post-hypnosis. A p-value <0.05 was considered statistically significant.

Moreover, significant differences in cold and heat pain thresholds was found for both the pain and analgesia groups. The pain group presented a decrease in heat pain threshold (HPT, pre: 44.59±3.898/post: 39.21±4.428, p=0.004 – Table 3) after hypnosis, which means that they began to feel pain earlier, responding to the painful stimulus at lower temperatures than in the pre-hypnosis. The same behavior occurs for the cold stimulus, the pain group also presented a decrease in cold pain threshold (CPT, pre: 12.58±10.583/post: 23.08±7.243, p=0.008 – Table 3) after hypnosis. Thereby, for assessing cold pain, the thermode temperature (t) varies between 32 to 0 Celsius degrees, meaning that once again, the subjects began to feel pain earlier, responding to the painful stimulus at lower temperatures than in the pre-hypnosis. In contrast, no significant changes were observed in the exteroceptive sensation of the sham group, even for warm or cold sensations.

The analgesia group showed an opposite frame with the subjects who were hypnotized to not feel pain presenting an increase of heat (HPT, pre: 41.51±3.456/post: 45.48±3.251, p=0.018 – Table 3) and cold pain thresholds (CPT, pre: 18.28±8.290/post: 14.31±10.310, p=0.034 – Table 3) after specific hypnotic suggestion. This means that they respond to pain stimulus later, being conditioned to withstand temperature changes**.**

Pain intensity was also assessed based on the VAS. For thermal stimuli, a variation in temperature occurred at 46-48˚C for warm sensation and at 10-5˚C for cold sensation. These temperatures can induce thermal hyperalgesia in both cases. Variations in pain intensity were positive for the pain group after hypnosis (WST, pre: 38.65±30.862/post: 54.00±27.575, p=0.009; CST, pre: 38.90±30.623/post: 55.15±27.633, p=0.008 – Table 3) for both warm and cold suprathresholds. However, it was negative for the analgesia group (WST, pre: 45.64±26.087/post: 31.07±26.168, p=0.018; CST, pre: 41.50±26.229/post: 29.35±26.305, p=0.018 – Table 3) at all assessed temperatures. Such results indicate that the volunteers hypnotized to feel pain indeed reported hyperalgesia after specific hypnotic suggestion, meanwhile the pain intensity was lower for the analgesia group. No difference was observed for the sham group, neither warm nor cold suprathresholds.

DISCUSSION

In this study, hypnosis was applied to healthy participants, who presented low risk for alcohol abuse or were abstinent, respecting the inclusion criteria. The sample was focused on healthy individuals that presented null or very low pain scores, making them eligible for the study. Data presented herein revealed that specific hypnotic suggestions altered exteroceptive sensitivity, either mechanical or thermal, for both pain and analgesia in healthy subjects. Regarding mechanical nociception, the results indicate that hypnosis was able to induce hyperalgesia and allodynia in the pain group, resulting in intensification of pain. On the other hand, the analgesia group became less sensitive to repeated induction of pain stimuli after hypnosis. Hypnosis can be considered as a procedure in which an intentional introspective mental activity is induced and guided by a hypnotherapist that engenders relevant changes of experience and bodily functions[32]. Hypnosis is known as a therapy that can intentionally change sensory inputs, feelings, mental representations, and behavioral and neurovegetative responses[33].

Regarding sensory inputs, hypnosis is considered a powerful analgesic tool, able to increase the pain threshold up to the level of surgical anesthesia[1,13] as well as modulate proprioceptive and sensory, nonpainful, inputs[34,35]. The results of this study demonstrate that specific hypnotic suggestions increased pain thresholds in the analgesia group after both heat and cold stimulations, meaning that these subjects became more resistant to pain sensations after hypnosis. In addition, it decreased pain thresholds in the pain group after both heat and cold stimulation, causing those individuals to be less resistant to pain. These data agree with those from randomized controlled studies demonstrating that hypnotic suggestion could improve pain conditions and analgesia[27,36].

The results of this study also indicated that hypnotic suggestion might be an effective procedure for alleviating pain perception in experimental models[37,38]. However, no changes were observed for the detection parameters of basal thresholds neither for the pain nor the analgesia group. These results can be related to the hypnotic suggestion being made on participants to induce either pain or analgesia, thus interfering with sensory, while detection thresholds should remain unchanged once hypnosis was supposed to change only pain perception and not basal sensitivity. These data are supported by clinical studies demonstrating that hypnotic relaxation without a specific analgesic suggestion result in thermal and mechanical detection, but not pain threshold changes, thus demonstrating that a relaxation suggestion has no genuine effect on sensory pain thresholds[39]. Herein, this study administered hypnotic suggestions, once subjects were specifically hypnotized to feel pain, revealing that specific suggestions are essential to hypnosis's effect on pain sensitivity. The exact mechanisms by which hypnosis can change pain perception are still being subjected to research, however, significant changes were revealed by functional magnetic resonance imaging (fMRI) in the insula, prefrontal, parietal, and anterior cingulate (ACC) cortices, areas involved in painful modulation[40,41], thus demonstrating that these regions influence pain thresholds.

It is worth highlighting that the quantitative sensory test (QST) is a psychophysical method that allows quantifying positive and negative phenomena of exteroceptive sensitivity transmitted by the thin or thick fibers of the peripheral nervous system (PNS)[22,23]. This instrument has been widely used in studies that are focused on explaining and understanding how pain mechanisms work, such as in neuropathic pain or orofacial pain, for example[28,42], enabling to examine both cutaneous and deep pain sensitivity, including cerebral processing of nociceptive data, to create sensory profiles by applying painful stimuli[28]. However, hypnosis does not specifically affect one kind of peripheral afferent nerve fiber but has an impact on the central processing of perception[38], as previously related.

The literature demonstrates that pain reduction has been more effective in individuals considered highly susceptible to hypnosis[19,20]. The results of this research agree with the literature since most subjects (n=19, 70.4%) presented moderate to high susceptibility scores spread across the different groups, responding to pain or analgesia in healthy individuals subjected to specific hypnotic suggestion.

The present study was able to demonstrate that specific hypnotic suggestion alters both mechanical and thermal exteroceptive sensitivity evaluated by QST, widely used to investigate somatosensory sensitivity, evaluating the functions of sensory nerve fibers A-δ and C of healthy volunteers. This finding is considered a great start in the search of how hypnosis could be useful in individuals with pain. The exact mechanisms by which hypnosis alters sensory functions are not yet fully understood and are part of the authors› future goals. Therefore, perception modification mainly for analgesia in healthy individuals broad out the idea to use hypnosis in refractory patients who will not answer appropriately in conventional treatment for chronic pain. Moreover, further investigations into these individuals would enlighten and enable its application in clinical practice.

CONCLUSION

Data presented herein demonstrate that specific hypnotic suggestions can modulate peripheral nociception in healthy subjects, revealing its modulatory effect both for pain and analgesia, in addition to enabling discussions for further studies on its clinical applicability.

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AUTHORS' CONTRIBUTIONS

Victória Regina da Silva Oliveira
Statistical Analysis, Data Collection, Conceptualization, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing
Inaeh de Paula Oliveira
Data Collection, Research, Writing - Preparation of the Original
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Data Collection, Research, Writing - Preparation of the Original
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Funding Acquisition, Conceptualization, Resource Management, Project Management, Writing - Preparation of the original, Writing - Review and Editing, Supervision

SUPLEMENTARY MATERIAL

1. Consort A

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on page number
Title	Effects of specific hypnotic suggestions on mechanical and thermal sensitivity of healthy volunteers: randomized and double-blind study	1
Authors *	Camila Squarzoni Dale (e-mail: camila.dale@usp.br) – corresponding author	1
Trial design	N/A	
Methods		
Participants	27 volunteers were enrolled in this study. Inclusion criteria: 18-65 years and absence of complaints of pain or psychological disorders. Non-inclusion criteria: subjects with a history of major psychiatric disease, substance abuse, or those unable to understand the consent form, individuals complaining of pain, and severe systemic, metabolic, or neurological disease capable of influencing quantitative sensory testing (QST).	2,5
Interventions	Specific hypnotic suggestions (hypnosis-induced pain and hypnosis-induced analgesia)	2,5
Objective	To evaluate the mechanical and thermal nociception after the specific hypnotic suggestions technique in healthy volunteers.	2,5
Outcome	specific hypnotic suggestions capable of alters the mechanical and thermal nociception in healthy subjects, revealing its modulatory effect both for pain and analgesia	2, 12-14, 16
Randomization	Computer-generated randomization (Excel software) was used to assign participant to three different groups: a) sham group (no induction of hypnosis), b) hypnosis-induced pain group, c) hypnosis-induced analgesia group	2,5
Blinding (masking)	the hypnotherapist was blinded to participant hypnosis susceptibility score, and the outcome assessor was blinded to group allocation.	2,5
Results		
Numbers randomized	a) sham group (no induction of hypnosis) = 9 b) hypnosis-induced pain group = 11 c) hypnosis-induced analgesia group = 7	2,11
Recruitment	advertisements posted in the university (USP)	2
Numbers analysed	a) sham group (no induction of hypnosis) = 9 b) hypnosis-induced pain group = 11 c) hypnosis-induced analgesia group = 7	2,11
Outcome	a) no significant changes were observed in the exteroceptive sensation of the sham group, even for warm or cold sensations, b) hypnosis was able to induce mechanical hyperalgesia and decreased thermal pain thresholds in hypnosis-induced pain group, c) hypnosis increased thermal pain thresholds in hypnosis-induced analgesia group.	12-16
Harms	No	
Conclusions	specific hypnotic suggestions could alter the mechanical and thermal nociception in healthy subjects, revealing its modulatory effect both for pain and analgesia response.	16
Trial registration	N/A	
Funding	Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP): [Grants 2016/10372-0; 2018/18483-1] and [Grant 2018/14560-1]. Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq): [Grant 830928/1992-8] and [Grant 156313/2018-9]	17

2. Tidier (Template for Intervention Description and Replication)

TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*
Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
1.	**BRIEF NAME** Specific Hypnotic Suggestion.	7	
2.	**WHY** Hypnosis is considered a psychological intervention to treat diseases such as depression, obesity, and phobias, and is one of the oldest forms of pain management.	4	
3.	**WHAT** The subject remained seated in a comfortable chair, at your disposal is a headphone and paper and pen to be used when necessary/requested.		
4.	Before hypnosis starts the hypnotic susceptibility test was applied by hypnotherapist. The procedure was verbally standardized through a headphone containing four sensorial families: psycho-imaginary, psycho-conflictive, polyvalent, and sensorial. After 20 minutes of hypnotic induction, the presentation of 12 hypnotic suggestions (1. Hand lowering; 2. Moving hands together; 3. Mosquito hallucination; 4. Taste hallucination; 5. Arm rigidity; 6. Dream about hypnosis; 7. Arm immobilization; 8. Age regression; 9. Music hallucination (hear jingle bells); 10. Negative visual hallucination; 11. Posthypnotic suggestion (draw a doodle of a tree on the response booklet), and 12. Posthypnotic amnesia). All participants were subjected to the hypnotic susceptibility scale to be classified as low (0–3 points), moderate (4-8 points), or high (9-12 points) susceptibility to hypnosis according to their score. After this, the hypnotic suggestion for pain or analgesia were applied. The hypnosis protocol consisted of two phases: induction and hypnotic suggestions. The standard hypnotic protocol began with an induction that is associated with breathing and relaxation, where subjects received suggestions to focus their attention on a single stimulus until reaching a trance state. This phase lasted around 10 minutes. After the induction, the hypnotic suggestions phase started, working on the imaginary, giving color, size, and shape to the sensation referred according to the hypnotic suggestion for pain and analgesia was given targeting the increase and decrease of the subject's pain and controls over their sensations in those groups, rescuing and using an interpretation already known to the hypnotized person.	6-7	
5.	**WHO PROVIDED** Qualified hypnotherapist. Technical training and clinical experience were required.	7	
6.	**HOW** Hypnosis was delivery in a face-to-face format with the presence of a hypnotherapist, it was also provided individually.	7	
7.	**WHERE** Non sophisticated infrastructure was required, only a quiet room with a comfortable chair.	6-7	
8.	**WHEN and HOW MUCH** Hypnosis was applied just once, for 20 minutes divided in two phases: induction and hypnotic suggestion, 10 minutes each.	7	
9.	**TAILORING** The procedure was designed to be applied in a similar way to each volunteer. Except for the fact that the hypnotherapist would only find out in the time of application what kind of hypnotic suggestion he would do whether to induce pain, analgesia or nothing (sham).	5	
10.‡	**MODIFICATIONS** No modifications were necessary.		
11.	**HOW WELL** The intervention adherence or fidelity was not assessed. All volunteers were eligible for the study.	5.9	
12.‡	The intervention adherence or fidelity was not assessed. All volunteers were eligible for the study.	5.9	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomized trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

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