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Placebo or Nocebo Interventions as Affected by Hypnotic Susceptibility

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Abstract: The purpose of the present study was to examine placebo and nocebo effects under hypnotic analgesia in lowly hypnotizable (LH) and highly hypnotizable (HH) subjects. A placebo and nocebo, obtained in a two-step intervention (verbal expectation and conditioning), were studied in 12 LH and 12 HH subjects under hypnosis. Visual analog scales (VASs) of pain intensity were recorded in response to short, painful electrical stimuli. VAS scores of placebo-produced analgesia differed significantly from nocebo-produced hyperalgesia in the LH subjects. Placebo intervention combined with hypnotic analgesia in LH subjects led to an analgesic degree similar to that achieved in the HH subjects. Yet, no difference was detected between the placebo and the nocebo effects on the HH subjects. Expectations for placebo and nocebo were significantly higher in the LH subjects than in the HH subjects. It seems that the HH subjects were more "tuned" to an inner trait that made them less susceptible to contextual cues, and therefore, more resistant to placebo/nocebo interventions. The ability to achieve hypnotic analgesia in LH subjects to the degree reached in the HH subjects under combined placebo intervention and hypnosis induction is of clinical significance. Combining placebo intervention with the induction of hypnotic analgesia could markedly improve analgesia, regardless of the patients' hypnotic susceptibility.

Keywords: placebo/nocebo suggestibility; placebo/nocebo–hypnosis interaction; expectation; conditioning; hypnotic susceptibility

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1. Introduction

The non-pharmacological treatment of pain reflects the growing appreciation for the role that these interventions play in the therapeutic armamentarium for pain management [1]. Hypnosis was shown to be remarkably effective at alleviating both clinical and experimental pain [2]. A recent meta-analysis demonstrated the effectiveness of hypnotic susceptibility, with a 42% reduction in the intensity of pain in subjects with high hypnotic susceptibility [3]. Hypnotic analgesia significantly exceeded the effect of a placebo in highly hypnotizable (HH) subjects by utilizing ischemic pain [4,5]. Painful electrical tooth-pulp stimulation had its painfulness markedly reduced under hypnotic analgesia in HH subjects, where the reduction significantly exceeded that of a placebo [6]. Focused hypnotic analgesia and hypnotic generalized relaxation produced differential hypnotic analgesia in response to ascending stimulus intensity, where the analgesic effect of the focused analgesia by far exceeded that of generalized relaxation in HH subjects but not in lowly hypnotizable (LH) subjects [7]. Furthermore, hypnotic relaxation demonstrated a constant pain reduction at all stimulus levels comparable to that under placebo analgesia [6]. It seems that generalized hypnotic relaxation evokes a sensory response similar to a placebo and bears no clear relationship to hypnotic susceptibility [7]. The interrelationship between hypnotic and placebo analgesia was further investigated in HH and LH subjects using two components of hypnotic analgesia: a local focus analgesia and a remote widespread analgesia [8]. It

was found that pain reduction produced in the local site was significantly higher in HH subjects than in the remote site, but it did not differ in the LH group [8]. It was concluded that focused hypnotic analgesia in HH subjects was related to hypnotic suggestions, while the remote widespread analgesia was independent of hypnotic susceptibility and possibly a placebo effect [8–10]. Hypnotic analgesia differs from placebo analgesia in its underlying mechanisms. Thus, placebo analgesia is naloxone-reversed, pointing to the production of endogenous opiates, while hypnotic analgesia is not reversed by naloxone [11–14]. Recently, De Pasacalis demonstrated that hypnosis is not equal to a common placebo in terms of brain activity, thus questioning the hypothesis that the pain-reducing properties of hypnosis are just one form of a placebo effect [15].

Expectations for pain relief are likely to play a major role in the mechanisms of a placebo, and conditioning procedures that induce placebo analgesia are mediated by expectation [16–18]. Conditioning can be attained by the pairing of surreptitiously lowered pain stimulus intensity with placebo administration, which results in subsequent placebo analgesia [19]. It seems that verbally induced expectations of analgesia alone are not as effective as when paired with a conditioning procedure; the latter is believed to increase the expectation of analgesia [20].

Mechanisms underlying the placebo effect were widely studied, but its opposite effect, the nocebo, has only recently attracted attention [21–23]. Placebo and nocebo effects are not just identical opposites, and verbally induced expectations and conditioning procedures do not have the same effects on a placebo and a nocebo [24]. Conditioning was of great importance and the verbal information was of much smaller importance in the placebo group, while conditioning did not contribute to any significant nocebo effect [24,25]. The fact that hypnotic analgesia is apparently not dependent on expectation [7,8] makes the study of expectation and conditioning as related to a nocebo, a placebo, and hypnotic analgesia even more attractive.

Hypnotic analgesia in HH subjects differs from that in LH subjects, but it is not clear whether HH subjects differ from LH subjects in their response to placebo analgesia or, for that matter, to nocebo hyperalgesia. Some studies suggested that HH and LH subjects may not differ in their response to placebo analgesia [4,26,27]. However, Hilgard and Hilgard [28] demonstrated that for HH subjects, the placebo response was negligible. Furthermore, HH subjects displayed significantly greater pain reduction than LH subjects in all experimental conditions except with the placebo [26]. Recently, it was demonstrated that in HH participants, a placebo treatment produced significant reductions in pain and distress perception in both waking and hypnosis conditions [15]. However, during the hypnotic–placebo analgesia in these HH subjects, the association of pain expectation with pain or distress reduction was weakened and not significant [15]. This was probably because HH subjects have more effective sensory filtering, or gating, of irrelevant stimuli than LH subjects [29]. This may be due to filtering or gating in HH subjects that may avert their attention from an "irrelevant" suggestion, such as placebo or nocebo effects, and make them less amenable than LH subjects to placebo or nocebo suggestions under hypnotic induction. The relationship between placebo/nocebo suggestibility and hypnotic susceptibility clearly needs further exploration, especially considering that the placebo and nocebo effects can affect almost any medical symptom, including pain [18].

The purpose of the present study was to test the hypothesis that placebo and nocebo suggestions, under hypnotic induction, will have a larger effect on LH subjects than those achieved in HH subjects.

2. Methods

2.1. Subjects

The subjects were adult (>18 years old), healthy, paid volunteers that were recruited using a posted announcement. Subjects were screened and allocated to highly hypnotizable (HH) or lowly hypnotizable (LH) groups using the "six-minute arm levitation test" (SHALIT) [30], which is a method that was successfully used by us in previous studies [6–

8]. This method allowed for the segregation of subjects using approximately the upper 30% and the lower 30% on the spectrum of hypnotic susceptibility according to the Stanford Hypnotic Susceptibility Scale, Form A (SHHS:A) [30]. The HH group consisted of 12 subjects (4 males, 8 females; mean age 27.8, range 21–42) and the LH group consisted of 12 subjects (5 males, 7 females; mean age 25.5, range 22–35).

We notified the subjects that they met the criteria for inclusion "in a study on the effect of hypnosis on pain, produced by very short electrical stimuli to the skin, to be compared with the effect of an anaesthetic or a sensitizing cream". Subjects then rated their expectation for pain reduction under hypnosis on a scale of 0 to 10, where zero meant no effect at all and 10 meant the maximum effect possible. We did not inform subjects whether they were in the HH or LH group in order not to bias their expectations.

2.2. Electrical Stimuli

We delivered painful stimuli via a pair of surface electrodes placed 2 cm apart on scrubbed, degreased skin of the volar aspect of the left arm. Stimuli consisted of a train of 10 pulses, with each pulse being 0.8 ms long with a 0.2 ms interpulse interval, with an interstimulus interval of 18–20 s, from a constant current isolation unit stimulator (Iso-Flex AMPI). Subjects were given stimuli of ascending and descending intensity and sensory and pain thresholds were determined according to the method of limits. We then delivered ascending stimuli up to a point tolerated by the subject; this point established the pain tolerance level. The experimenter who delivered the stimuli was blind to the hypnotic susceptibility of the subjects.

2.3. Assessment of Sensation

After each stimulus was delivered, the subject graded the intensity of the sensation evoked on a 100 mm visual analog scale (VAS); the end-points on the line were marked "no sensation" and "strongest possible sensation".

2.4. Placebo/nocebo Cream

We applied an inert cream colored using food colors, blue for placebo and red for nocebo, around the stimulating electrodes according to the experimental design (see below). We informed the subject that the cream has a proven effect for decreasing (or increasing in the case of the nocebo) the pain sensation, and its *physiological* effect is to be compared with the *psychological* effect of hypnosis.

2.5. Experimental Design

Two counterbalanced sessions, a week apart, were conducted for each subject, one with a placebo cream and the other with a nocebo cream. The following steps took place at each session:

1. Establish and rate the experimental stimulus intensity. We measured the pain threshold and pain tolerance (see above), and the subject marked each for pain intensity on a visual analog scale (VAS). We then established the *experimental stimulus intensity* (ESI) as halfway between the pain threshold and pain tolerance and delivered it once. We told the subject that this stimulus intensity would not change throughout the experiment. However, pain sensations may change according to experimental conditions, i.e., hypnosis or cream application. The ESI was then delivered six times and pain sensations were marked by the subject on a VAS for pain intensity.

2. Rate the expectation with hypnotic analgesia. Subjects were asked to rate the expectation for pain reduction under hypnosis on a scale of 0 to 10, where zero means no effect and 10 means the maximum.

3. Produce expectations with the placebo/nocebo. We rubbed the "conditioning cream" around the stimulating electrodes. We explained that this anesthetic (or sensitizing) cream has a clear and proven *physiological* effect of decreasing (increasing) pain, which was to be compared with the *psychological* effects of pain reduction under hypnosis.

4. Rate the expectation with the placebo/nocebo. Subjects were asked to rate the expectation for pain reduction (or elevation) produced by the cream on a scale of 0 to 10.

5. Produce conditioning to the placebo/nocebo. We surreptitiously reduced (or increased) the ESI to 70% (or to 130%) in order to produce conditioning. The current was decreased (or increased) in two stages: by 15% for 5 stimuli and another 15% for the next 5 stimuli. We informed the subject that the cream needed time to penetrate and we wanted to know when it became effective. At each stimulus, the subject reported whether a change in intensity occurred, but did not mark it on a VAS.

6. Rate the conditioning of the placebo/nocebo. Subjects were asked to rate the expectation after conditioning for pain reduction (or elevation) produced by the cream on a scale of 0 to 10.

7. Measure the placebo/nocebo effect. The ESI was repeated six times and pain sensations were marked on a VAS for pain intensity.

8. Induce hypnotic relaxation. Hypnotic relaxation was induced for about 8 min according to a well-established procedure, as detailed below [7,8].

9. Measure the effect of hypnotic relaxation after giving the placebo/nocebo. The ESI was repeated six times and pain sensations were marked on a VAS for pain intensity.

10. Induce hypnotic analgesia. Focused hypnotic analgesia was induced for about 8 min according to a well-established procedure, as detailed below [7,8].

11. Measure the effect of hypnotic analgesia after giving the placebo/nocebo. The ESI was repeated six times and pain sensations were marked on a VAS for pain intensity.

12. Measure the effect of the placebo/nocebo after hypnotic analgesia. Subjects were instructed to exit the hypnotic state and were reminded that the anesthetic/stimulating cream was still effective. The ESI was repeated six times and pain sensations were marked on a VAS for pain intensity.

2.6. Induction of Hypnotic Relaxation

Induction of hypnotic relaxation included the following:

1. Physical relaxation: "you start to feel relaxed and loosen up, your feet . . . your legs . . . your knees . . . belly . . . shoulders . . . head . . . all your muscles are loosening up. You have a feeling of warmth, heaviness, and deep relaxation all over your body, you sit relaxed, calm".

2. A feeling of tranquility and restfulness: "and although you are aware of my voice, you are now more aware of the feeling of tranquility, you feel calm and peaceful, as you continue enjoying the restfulness of not having to do anything in particular right now".

3. Relaxing guided imagery: "you are now in a place where you feel calm and relaxed; maybe in a garden with a lawn and trees. Under the trees there are reclining chairs, you choose one and sit. You look upward and can see the leaves glittering in the sun, the blue sky, you feel totally relaxed . . . calm . . . secure and peaceful".

4. Normal sensation with continued relaxation: "and although you continue to experience normal sensation . . . your experience seems surprisingly more pleasant, surprisingly more pleasant than you would expected, surprisingly more relaxed . . . surprisingly more relaxed than you would have expected".

5. Feeling relaxed at the time of the stimuli: "and I want to remind you that when you felt the stimulus, you were mindful of its intensity, but now you know how calm and relaxed you can feel. Almost as if, when you feel the onset of stimulus, you can feel an onset of relaxation . . . quickly spreading all over your body . . . and you become even more calm . . . more relaxed".

2.7. Induction of Hypnotic Analgesia

1. Continuation of a relaxed state: "Return now to your reclining chair under the tree in the garden, look up, and see the leaves glittering in the sun, and the deep blue sky, you feel totally relaxed . . . calm . . . secure and peaceful . . . ".

2. *Normalization of analgesia:* "and it is interesting to notice that while you are listening to me you have forgotten that you have a right hand . . . and yet now you can feel it. You forgot that you could sense your legs, and now you can feel them. We've all tremendous experience in developing anesthesia in all parts of our body, as if we can forget and ignore parts of our body, and what we feel depends very much on us".

3. *Reduction of stimulus intensity:* "We remember that we have a stimulating device, that by rotating its button we can increase the intensity of the stimuli. Now, at the same time you can imagine that you have a button of your own, a button of sensation, that now you turn down in order to decrease your sensation . . . until you feel less and less . . . less and less".

4. *Creating focused anesthesia:* "As you know already, we can forget and ignore parts of our body, and stop feeling these parts. On the other hand, we can also concentrate on parts of our body and intentionally reduce the sensations in these parts. Concentrate now on your left hand, where the stimulating electrodes are attached. You may start feeling some different sensation at that part, may be a tingling, perhaps it starts to feel numb similar to what you may sense under a local anesthetic. A feeling you can enjoy now, as you feel that your left arm is becoming more and more numb".

For the sake of uniformity, the hypnotic induction was carried out by the same investigator (Y.S.) and identical instructions, which were read from a preprepared manuscript, were given to each subject.

3. Statistical Analyses

All the analyses were performed using the SAS® version 9.1 software (SAS Institute Inc., Cary, NC, USA); the alpha for significance was set at 0.05. The pain as assessed using a VAS score was analyzed using a repeated measures analysis (RMA) of the covariance model (SAS® MIXED procedure). The analysis, which aimed to compare the VAS score between the treatments received (placebo or nocebo) and between the hypnotizability levels, included the following fixed effects: treatment (placebo/nocebo), stage of the experiment (basis, post-conditioning, hypnotic relaxation, hypnotic analgesia, post-hypnosis), hypnotizability (LH/HH), interaction of stage by treatment, and interaction of hypnotizability by stage by treatment. The statistical tests comparing the adjusted means (LSMEANS command with PDIFF option) were obtained from the above model. The expectation for hypnotic analgesia was compared between the hypnotizability levels using the Kruskal–Wallis non-parametric test (SAS® NPAR1WAY procedure). The difference between the treatments was compared at each experiment stage with a signed rank test (SAS® UNIVARIATE procedure). No adjustment for multiple testing was done.

4. Results

4.1. Placebo and Nocebo Effects

Repeated measures analysis demonstrated that the treatment, stage of the experiment, and hypnotizability were statistically significant ($p < 0.004$). The interaction of stage by treatment approached significance ($p = 0.075$), and adding hypnotizability to this interaction made it highly significant ($p < 0.0001$, Table 1).

The effects of the placebo and nocebo differed significantly in the LH subjects at each of the experimental stages ($p < 0.0001$). The placebo conditioning resulted in significantly lower VAS ratings compared with the nocebo conditioning. This was noticed at the post-conditioning (pre-hypnotic) stage, and thereafter, under hypnotic relaxation, hypnotic analgesia, and in the post-hypnotic stage (Table 2, Figure 1). However, no such difference was apparent between the effects of the placebo and nocebo for HH subjects at any of the experimental stages. The HH subjects, contrary to the LH subjects, reacted similarly to the placebo and nocebo manipulations (Table 2, Figure 2).

Table 1. Repeated measures analysis of the pain intensity VAS scores between treatments at various experimental stages in the lowly hypnotizable (LH) and highly hypnotizable (HH) subjects.

Effect	DF	F-Value	*p*
Treatment (placebo/nocebo)	1	47.54	<0.0001
Stage of experiment	4	220.25	<0.0001
Hypnotizability (LH/HH)	1	10.58	0.0034
Stage * treatment	4	2.13	0.0748
Hypnotizability * stage * treatment	9	15.79	<0.0001

Table 2. Estimate of average pain intensity ± standard error, by lowly (LH) and highly hypnotizable (HH) subjects at different experimental stages under the placebo and nocebo conditions.

Highly/Lowly Hypnotizable	Experimental Stage	Placebo	Nocebo	*p*-Value
LH	Baseline	55.85 ± 2.37	55.65 ± 2.29	0.9113
	Post-conditioning	50.47 ± 2.43	60.93 ± 2.41	<0.0001
	Hypnotic relaxation	37.97 ± 1.82	49.90 ± 2.07	<0.0001
	Hypnotic analgesia	31.26 ± 1.82	43.75 ± 2.35	<0.0001
	Post-hypnosis	43.24 ± 1.80	58.03 ± 2.50	<0.0001
HH	Baseline	56.39 ± 1.37	54.62 ± 1.50	0.3121
	Post-conditioning	54.39 ± 1.18	54.10 ± 2.39	0.8672
	Hypnotic relaxation	38.72 ± 1.55	37.03 ± 1.64	0.3315
	Hypnotic analgesia	29.68 ± 1.30	27.61 ± 1.62	0.2357
	Post-hypnosis	40.14 ± 1.62	43.24 ± 2.15	0.0760

4.2. Expectation

4.2.1. Expectation for Hypnotic Analgesia

At the time of screening, the HH subjects had a higher expectation for hypnotic analgesia than the LH subjects ($p = 0.004$, Table 3). However, this difference was not present during the placebo or nocebo experimental sessions ($p = 0.094$ and 0.084, respectively). In addition, no correlation could be detected between the expectation for hypnotic analgesia and VAS scores under hypnotic analgesia when analyzed for the LH and HH subjects ($p = 0.20$ and 0.31, respectively).

4.2.2. Expectations for Placebo and Nocebo Effects

Verbal expectation. Verbal expectation (cream application) produced a significantly higher expectation for a placebo effect on the LH subjects compared with the HH subjects, but not for a nocebo effect (($p = 0.007$ and 0.315, respectively; Table 3).

Conditioning. Contrary to verbal expectation, conditioning produced minimal differences between the LH and HH subjects regarding the expectation for a placebo effect, but there was a significant difference in expectation for a nocebo effect ($p = 0.406$ and 0.043, respectively).

Verbal expectation compared with conditioning. No difference was found between the verbal expectation and conditioning within the LH and HH groups within the placebo ($p = 0.13$ and 0.55, respectively) and nocebo sessions ($p = 0.72$ and 0.07, respectively).

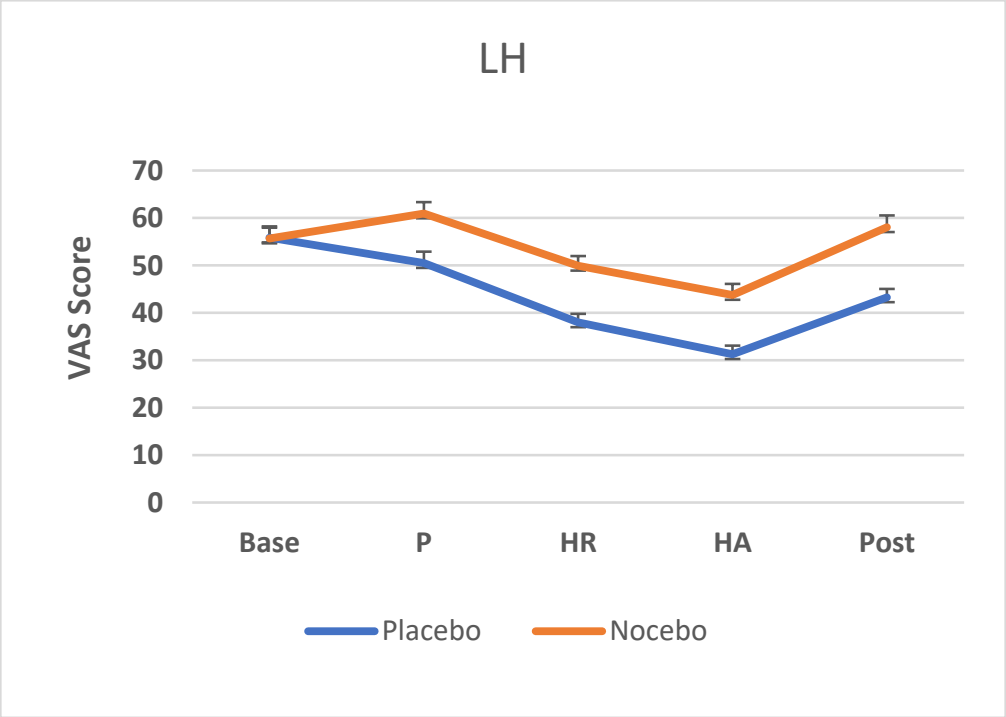


Figure 1. VAS scores for painful stimuli in the lowly hypnotizable (LH) subjects after the placebo or nocebo conditioning. Base—baseline scores before placebo or nocebo manipulations; P—after placebo/nocebo conditioning; HR—hypnotic relaxation; HA—hypnotic analgesia; Post—post-hypnosis but still under placebo/nocebo effects.

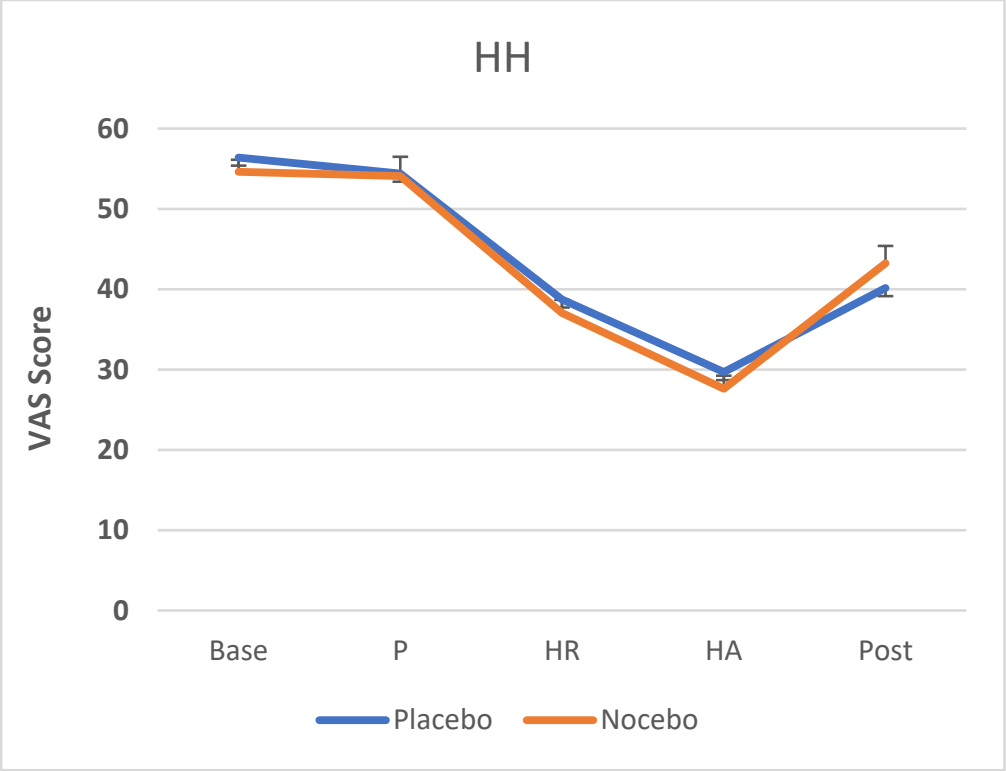


Figure 2. VAS scores to painful stimuli in the highly hypnotizable (HH) subjects after placebo or nocebo conditioning. Base—baseline scores before placebo or nocebo manipulations; P—after placebo/nocebo conditioning; HR—hypnotic relaxation; HA—hypnotic analgesia; Post—post-hypnosis but still under placebo/nocebo effects.

Table 3. Average expectation rates ± standard error for analgesia (for hypnotic and placebo conditions) or hyperalgesia (for nocebo condition) from the highly (HH) and lowly hypnotizable (LH) subjects.

Condition	LH	HH	*p*-Value
Hypnosis (at screening)	4.45 ± 0.67	6.91 ± 0.34	0.004
Hypnosis (during session)			
Placebo	4.25 ± 0.66	5.79 ± 0.59	0.094
Nocebo	4.70 ± 0.65	6.20 ± 0.55	0.084
Cream application			
Placebo	7.54 ± 0.49	5.54 ± 0.46	0.007
Nocebo	6.95 ± 0.72	5.95 ± 0.65	0.315
Conditioning			
Placebo	6.59 ± 0.56	5.87 ± 0.62	0.406
Nocebo	7.17 ± 0.82	5.00 ± 0.55	0.043
Cream + conditioning			
Placebo	7.08 ± 0.38	5.71 ± 0.38	0.045
Nocebo	7.06 ± 0.54	5.50 ± 0.43	0.081
Placebo + nocebo			
Cream	7.25 ± 0.43	5.75 ± 0.39	0.032
Conditioning	6.89 ± 0.50	5.45 ± 0.42	0.033

Verbal expectation and conditioning combined. When the effects of verbal expectation and conditioning were averaged for each subject (Table 3), the LH subjects demonstrated a higher expectation than the HH subjects for a placebo effect, but not for a nocebo effect (p = 0.045 and 0.081, respectively).

Expectations for placebo and nocebo effects combined. When the effects of the placebo and nocebo were averaged for each subject, LH subjects showed a consistently higher expectation rate than the HH subjects for verbal and conditioning manipulations (p = 0.032 and 0.033, respectively; Table 3).

5. Discussion

Placebo and nocebo effects, produced in a two-step intervention (verbal expectation and conditioning), were studied under hypnotic analgesia in lowly (LH) and highly hypnotizable (HH) subjects. To the best of our knowledge, this is the only study in which placebo and nocebo effects were directly contrasted in LH and HH subjects under hypnotic induction. We examined placebo and nocebo effects under the four following settings: post-conditioning, hypnotic relaxation, hypnotic analgesia, and post-hypnosis. The VAS scores of placebo-produced analgesia differed significantly from nocebo-produced hyperalgesia at all experimental stages in the LH subjects (Figure 1 and Table 2). Placebo intervention combined with hypnotic analgesia in the LH subjects produced a significant elevation of analgesia, but nocebo did not reduce their hypnotic analgesia (Figure 3). Figure 3 demonstrates that the percentage of pain reduction in the LH subjects under placebo was similar to that achieved in the HH subjects under placebo or nocebo, as well as the HH subjects under no placebo/nocebo preconditioning.

Surprisingly, no difference was detected between the placebo and the nocebo effects on the HH subjects, and the HH subjects seemed unresponsive to any of the placebo or nocebo interventions (Figures 2 and 3, Table 2).

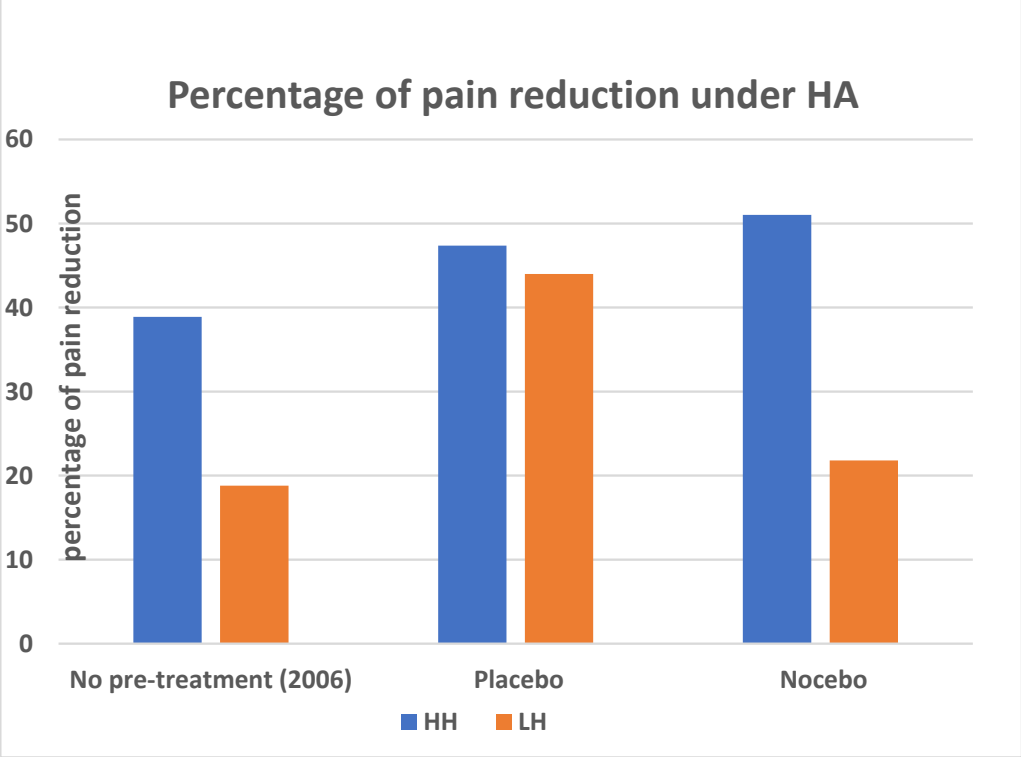


Figure 3. Percentage of pain reduction from the baseline VAS scores and under hypnotic analgesia (HA) in the highly hypnotizable (HH) and lowly hypnotizable (LH) subjects. A comparison was made between present data under placebo (Placebo) or nocebo (Nocebo) conditions and data with no preconditioning of placebo or nocebo (No pre-treatment (2006)) from Sharav and Tal [8]. The comparison is valid, as the subject selection and the focused hypnotic analgesia were reproduced in the present and the 2006 studies with comparable intensities by the same investigator (Y.S.).

5.1. Placebo and Nocebo Effects on the LH Subjects

Of special interest was the effect of the placebo pre-intervention on the enhancement of analgesia in this LH group under hypnosis. The amount of analgesia achieved after the placebo induction in the LH subjects during hypnotic relaxation and hypnotic analgesia was very similar to that achieved in the HH subjects (Table 2, Figure 3). This phenomenon may be of clinical benefit, as combining placebo intervention with the induction of hypnotic analgesia could markedly improve analgesia, regardless of the patient's hypnotic susceptibility [31]. Interestingly, such an enhancement of hypnotic analgesia could not be achieved by suggestions to "imagine glove anaesthesia" (a form of hypnotic suggestion) delivered before hypnotic induction in LH subjects [32]. Hypnosis is not equal to the placebo in terms of brain activity and pain-reducing properties [15], which may explain these different results. Therefore, we recommend that in order to enhance hypnotic analgesia in LH subjects, "placebo-hypnotic" interventions rather than "hypnotic-hypnotic" induction techniques should be utilized. This presumably additive effect of the placebo and hypnotic intervention could be similar to a possible interaction between placebo effects and drug effects (i.e., additivity assumption) [33]; this is especially true given that the added analgesia under placebo interventions was identical in the LH subjects at all hypnotic stages, which is reminiscent of the placebo equal pain reduction at ascending stimulus intensities [6].

While placebo manipulations enhanced the analgesic response under hypnosis in the LH subjects, the nocebo intervention did not seem to interfere with the analgesic effect of hypnosis in these subjects (Figures 1 and 3). This can be due to the assumption that conditioning was of great importance in the placebo effect, while conditioning did not contribute to any significant nocebo effect [24,25]. Since we intervened first with a

verbal suggestion to be followed by conditioning, the latter may have affected the placebo response but not the nocebo response. Apparently, a nocebo is not simply the opposite of a placebo; therefore, a placebo and a nocebo may not be "two sides of the same coin" [24,25].

5.2. Placebo and Nocebo Effects on the HH Subjects

The pain reduction under hypnotic analgesia in the HH subjects in the present study was similar to that of the HH subjects with no pre-conditioning, as found in our previous study (Figure 3) [8]. Unpredictably, highly hypnotizable subjects seemed to be totally unresponsive to any of the placebo or nocebo interventions (Figure 2, Table 2). The "indifference" of the HH subjects to external manipulation can, at least partially, be attributed to the experiential distinction ("outside authoritative" as opposed to "innate self-directed") between placebo and hypnotic analgesia, respectively [34], which may have contributed to their resistance to the "outside" placebo/nocebo effects. Additionally, the HH subjects have more effective sensory filtering, or gating, of irrelevant stimuli than the LH subjects [29]. This filtering outcome in the HH subjects may have averted their attention from "irrelevant" suggestions, such as placebo or nocebo manipulations, and made them less amenable than the LH subjects to their effects. In other words, the HH subjects were more "tuned" to an inner trait and therefore more resistant to any external interventions.

However, a placebo acts within a contextual situation, and our subjects were aware that hypnosis would follow the placebo/nocebo interventions. Such a contextual effect may have caused the HH subjects to activate an inhibitory control by "cross representation suppression", which blocked these external cues [35]. Our results were possibly limited to this experimental setup and the HH subjects might have responded to placebo or nocebo interventions differently in other situations, i.e., when not followed by hypnotic induction. The lack of a placebo effect on our HH subjects could also be associated with a decreased desire for pain relief due to tranquillity and harmony operating under hypnosis [9]. However, this seems improbable since the desire for pain relief is not significantly associated with the magnitude of placebo analgesia to brief heat stimuli, which was comparable to our short electrical stimuli [19].

5.3. Pre-Hypnotic Placebo and Nocebo Effects on the LH and HH Subjects

The difference between the LH and HH subjects was also apparent before hypnotic suggestions were implemented. Table 2 demonstrates the post-conditioning effects of the placebo and nocebo in the LH and HH subjects. In the LH subjects, a significant difference between the placebo and nocebo was observed, but not in the HH subjects. However, the placebo or nocebo interventions were performed within the same session in which hypnotic relaxation and hypnotic analgesia also took place, and the subjects were aware of this fact. This situation is discussed in Section 6: Limitations and Conclusions. Yet, even under these limitations, there was an a priori difference between the two groups in their response to placebo/nocebo interventions.

5.4. Expectation

Expectations for hypnotic analgesia at the screening and during sessions. The HH subjects had significantly higher expectations for hypnotic analgesia than the LH subjects did at the screening appointment, but no such difference was detected during the experimental sessions (Table 3). We believe that at the screening time, the HH subjects were under the effects of their successful arm levitation with a subsequent sense of higher absorption, and therefore, had higher expectations than the LH subjects had. At the experimental sessions, which was usually about two weeks later, the HH subjects' expectation decreased to some degree and was not significantly different anymore from that of the LH subjects.

Verbal expectation and conditioning. Based on previous studies, one would expect conditioning to increase the expectation regarding the placebo [16,17,19,20]. Furthermore, the effect of conditioning and suggestion seems to be additive, and at the end of the two-stage procedure (verbal and conditioning), we anticipated an increased level of expectation [36].

However, this did not occur in our study. Expectations for placebo analgesia and nocebo hyperalgesia produced by cream application (verbal expectation) did not differ from that produced by the subsequent conditioning manipulation in the HH or LH subjects (Table 3). It is our impression that conditioning did not augment the effect of verbal expectation because of our subject population. Most of our subjects came from a medically oriented background (medical, pharmacy, and dental students), and thus, they had a basic belief in medications at large, which was extrapolated to belief in the power of the cream (e.g., more than 7 on a scale out of 10 for the LH subjects). Thus, for example, they expected the placebo cream to act as an anesthetic cream that could eliminate sensation. When the surreptitious conditioning stimulus was applied (with a 30% change from the original stimulating current), we sometimes heard the subject say "Is that all?" with a tone of disappointment.

Verbal expectation and conditioning in the LH and HH subjects. The overall expectation level of the LH subjects was higher than that of the HH subjects; this was even clearer when the placebo and nocebo effects were combined (Table 3). This higher expectation rate may explain the responsiveness of the LH group to placebo and nocebo interventions and was in keeping with the mechanisms of placebo and nocebo associated with expectation [16,17,19].

6. Limitations and Conclusions

The highly hypnotizable (HH) subjects seemed unresponsive to the placebo or nocebo interventions, and hypnotizability was not synonymous with suggestibility. It seems that the HH subjects were more "tuned" to an inner trait that made them less susceptible to contextual cues, and therefore, more resistant to placebo/nocebo interventions. However, we performed placebo or nocebo interventions within the same session in which hypnotic relaxation and hypnotic analgesia also took place, and the subjects were aware of this fact. Consequently, "cross representation suppression" [35,37] could have blocked these external cues associated with placebo/nocebo interventions in the HH subjects. An experiment that examines these placebo/nocebo interventions in HH and LH subjects without employing hypnotic induction at the same session may elucidate this point.

Another limitation was the lack of an experiment of our subject under hypnosis with no placebo or nocebo interventions. We partially overcame this limitation by using our 2006 data (see Figure 3) to accommodate for this shortcoming. However, we are aware that this had all the limitations of using "historical controls".

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