Influences of hypnotic suggestibility, automaticity, pain expectation, and EEG alpha on placebo analgesia responsiveness

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Introduction and Hypotheses

One of the most studied phenomena is pain reduction consequent to placebo treatment. Pain and placebo analgesia (PA) effects are phenomena influenced by a number of variables as hypnotic and waking suggestibility, (i.e., the individual responsiveness to verbal and/or nonverbal suggestions), response expectancy, and experienced involuntariness/automaticity (Benedetti, 2014; Bowers, 1981; Corsi & Colloca, 2017; Gheorghiu, 2000; Kirsch, 2018; Oakley & Halligan, 2013). In the present double-blind study, after an initial PA manipulation condition, we measured lower and upper EEG-alpha sub-bands (namely, 'alpha1' and 'alpha2') power changes during waking and hypnosis under two treatments: (*i*) painful stimulation (Pain); (*j*) painful stimulation after application of a PA cream. We tested the role of hypnotic suggestibility, involuntariness, pain expectation, and subjective hypnotic depth in the prediction of placebo analgesia (PA) responsiveness. Further aims were: (1) to test the expected alpha band power increases to PA and highlight the alpha sub-band power changes sensitive to pain reduction (Nir et al., 2012) ; (2) to test the hypothesis, we derived from Blakemore et al. (2003) and Rainville et al. (2019) previous reports, that higher self-report involuntariness scores are associated with higher alpha activity changes in the parietal and frontal region of the scalp, being part of a frontoparietal network responsible for the sense of self-agency and volition (Darby et al., 2018). Finally, conditional to find a robust alpha sub-band predictor of PA, (3) we wanted to highlight presumed direct and indirect effects of this objective alpha measure in predicting pain reduction by using the contextual measures, as potential mediators.

Method (1)

Participants

56 right-handed women, university student volunteers (M=24.5, SD=2.5 years). This study was approved by the Institutional Review Board (IRB) of the Department of Psychology, La Sapienza University of Rome, in accordance with the Declaration of Helsinki.

Procedure

• ***First Experimental day***

Measures: (1) Stanford Hypnotic Susceptibility Scale, Form C (SHSS:C, N = 56, M= 6.4, SD = 3.4; Md = 6.0) (Weitzenhoffer A. M. & Hilgard E. R., 1962); (2) Italian version of the Edinburgh Inventory Questionnaire (Oldfield, 1971).

Method (2)

• ***Second Experimental day***

We first measured individual pain thresholds then administered a pain manipulation procedure, and finally EEG recordings. EEG was recorded during waking and hypnosis under two treatments: (*i*) painful stimulation (Pain); (*j*) painful stimulation after application of a PA cream. We induced hypnosis with the Stanford Hypnotic Clinical Scale (SHCS; N = 56, M= 2.4, SD = 1.6; Md = 2.0; Morgan & Hilgard, 1978-1979). We administered the following contextual rating scales: Pain Expectation, Hypnotic Depth, Involuntariness, Pain and Distress (0 – 100 numeric scales). State-trait anxiety inventory (STAY-Y1; Spielberger et al., 1999) after each experimental treatment. The numerical pain difference scores (NPDSs) was calculated by subtracting numerical pain scores (NPSs) rated during PA from scores rated during Pain.

EEG Recording

EEG data were recorded from 30 electrodes using the 10-20 system and stored on a Neuroscan Acquire 4.3. The electrode impedance was kept less than 5 kΩ. 40 artifact-free (2.048 s) epochs for Pain and PA treatments (sampling frequency = 256 Hz) were analyzed using FFT to calculate lower and upper alpha sub-band (i.e., ΔAlpha1 and ΔAlpha2) power changes. For each waking and hypnosis condition, we calculated these scores by subtracting alpha1 and alpha2 during Pain from those during PA. Within the conventional alpha band (7.5 – 12 Hz), alpha1 and alpha 2 sub-bands were calculated by using individual alpha frequency obtained using Klimesch (1999) method.

Statistical analyses

Pearson correlation coefficients were first obtained to examine the relationship of ΔAlpha1 and ΔAlpha2 with contextual variables as Pain Expectation, Hypnotic Suggestibility (SHCS), experienced Hypnotic Depth, and Involuntariness in PA responding. We tested parallel multiple mediator models evaluating the role of hypnotic suggestibility as the main predictor and contextual measures as mediators with state anxiety as a covariate. We also tested simple mediation models using an EEG-alpha measure as a predictor of the NPDSs and each contextual variable as a potential mediator (PROCESS macro; Hayes, 2013). False Discovery Rate (FDR) correction was applied.

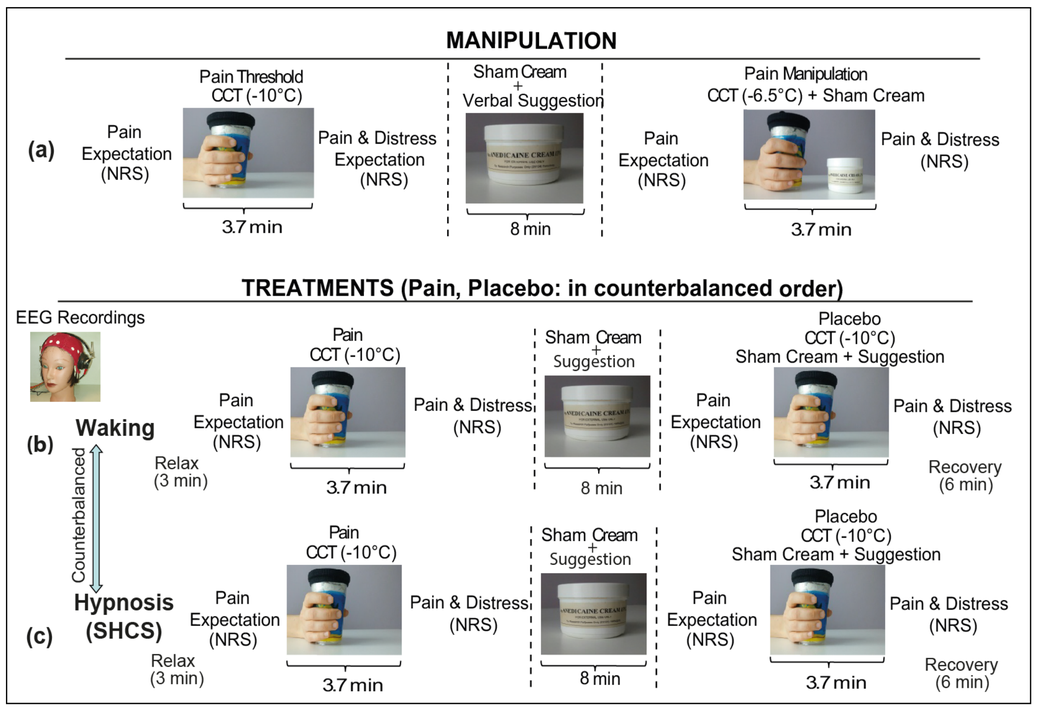

Fig 1. Schematic representation of experimental design and procedure. Panel (a) displays Manipulation procedure including the initial Pain Expectation rating, the measure of Pain Threshold, the administration of Sham Cream plus Verbal Suggestion and Pain Manipulation. In panel (b) are shown Pain and Placebo treatments in waking condition. In panel (c) are shown the same treatments administered after the hypnotic induction (Stanford Hypnotic Clinical Scale, SHCS).

Results

Pain and contextual measures

• NPSs obtained for PA were found significantly smaller than those for Pain treatment (see t-tests in **Table 1**), indicating that PA treatment was effective in pain reduction.

• We found significantly higher involuntariness scores during hypnosis than waking condition (t(55) = -2.51, p = 0.015).

• Pearson correlation, FDR corrected, coefficients among the measures of SHCS, contextual factors of interest and state anxiety with descriptive statistics are reported in **Table 2**. In waking W-NPDSs were significantly correlated with SHSC, experienced Hypnotic Depth, Pain Expectation, and Involuntariness scores. Interestingly, these significant relationships disappeared in hypnosis condition, except for Involuntariness in PA that continued to be significantly correlated with H-NPDSs.

Alpha1 and alpha2 power during waking and hypnosis

• For apha1 power, there was a relative tendency to increases during PA treatment (t < 0 in both waking and hypnosis), but none of them reached the FDR significance level. Instead, during waking condition, we found that alpha2 power at P3 scalp lead significantly increased during PA treatment (t(55) = -3.74, after FDR correction $p_{(FDR)}$ = 0.0015). During hypnosis condition we observed a significant apha2 increase at TP7 lead to PA as compared to Pain treatment (t(55) = -3.18, $p_{(FDR)}$ = 0.012).

• In waking condition, we obtained significant correlations for the only ΔAlpha2 power scores at TP8, T6 and P3, and in hypnosis for the ΔAlpha2 at TP7 scalp site (see **Table 3**).

• In hypnosis condition, none of the ΔAlpha2 measures of interest was significantly associated with pain reduction (H-NPDS) during PA treatment, although SHSC and Involuntariness in PA scores were negatively correlated with ΔAlpha2 at TP7 lead (lower quadrant of **Table 3**).

•→ Using mediation analyses we found in waking condition that: (i) hypnotic suggestibility influenced PA responding through the multiple mediation of pain expectation, involuntariness, and hypnotic depth (**Figure 2**); (j) the enhancement of relative left-parietal alpha2 power, directly influenced the enhancement in pain reduction, and, indirectly, through the mediating positive effect of involuntariness (**Figure 3**)

Descriptive statistics for Numerical Pain scores (NPS) and Involuntariness to PA during Pain and Placebo Analgesia (PA) treatments with t-test scores in waking (W) and hypnosis (H) conditions (N = 56).

Numerical Pain Scores (NPS)	*Waking*		*t (df=55)*	*p*	*Hypnosis*		*t (df=55)*	*p*	*Waking W-Involv. In PA*	*Hypnosis H-Involv. In PA*	*t (df=55)*	*p*
	Pain (W-NPS)	*PA (NPS)*			*Pain (H-NPS)*	*PA (NPS)*						
Mean	55.41	49.07	3.11	0.003	46.75	40.93	2.97	0.004	32.1	37.5	-2.51	0.015
SD	21.47	25.02	-	-	26.92	25.69	-	-	34.3	37.9		
Range	(17.5, 92.5)	(5, 100)	-	-	(0, 95)	(0, 90)	-	-				

TABLE 2

Correlations and descriptive statistics for pain difference score (Pain minus PA treatment) in waking (W-NPDS) and hypnosis (H-NPDS), hypnotic suggestibility (SHCS), and situational measures of interest

	1	2	3	4	5	6	7	8
1. W-NPDS	-							
2. H-NPDS	0.16	-						
3. SHCS*	0.39•	0.24	-					
4. Hypnotic Depth	0.41•	0.30	0.69†	-				
5. Pain Expectation	0.48•	0.22	0.35*	0.40•	-			
6. W-Involunt. in PA	0.54†	0.39•	0.47•	0.31	0.44•	-		
7. H-Involunt. in PA	0.52†	0.40•	0.56†	0.43•	0.41•	0.90‡	-	
8. State Anxiety	0.00	-0.14	-0.37*	-0.35*	-0.17	-0.02	-0.05	-
Mean	6.3	5.8	2.4	54.6	51.6	32.1	37.5	35.1
SD	15.2	14.7	1.6	26.2	22.0	34.3	37.9	6.0
Range	-25 - 45	-30 - 60	0 - 5	10 - 100	10 - 90	0 - 100	0 - 100	21 - 47

* Stanford Hypnotic Clinical Scale (SHCS; Morgan and Hilgard, 1978)

* p < 0.05; • p < 0.01; † p < 0.001; ‡ p < 0.0001; False Discovery Rate correction; N = 56 women

TABLE 3

Pearson partial correlation coefficients of pain minus placebo analgesia numerical pain rating score (NPDS), hypnotic suggestibility, and contextual factors of hypnotic depth, pain expectation, and involuntariness with pain minus placebo EEG-alpha2 power score (ΔAlpha2) at temporal and parietal scalp sites. Partial correlations are for waking (W; upper quadrant) and hypnosis condition (H; lower quadrant). The effect of state anxiety is partialled out.

	Waking Condition					
	ΔAlpha2 TP7	ΔAlpha2 TP8	ΔAlpha2 T5	ΔAlpha2 T6	ΔAlpha2 P3	ΔAlpha2 P4
W-NPDS	0.07	-0.33*	-0.09	-0.34*	-0.49†	-0.25
SHCS	-0.03	-0.28	-0.07	-0.25	-0.47•	-0.25
Hypnotic Depth	0.03	-0.23	0.03	-0.22	-0.24	-0.15
Pain Expectation	-0.17	-0.29	-0.24	-0.29	-0.37*	-0.27
W-Involunt. in PA	-0.09	-0.29	-0.20	-0.31	-0.47•	-0.22
Mean	-0.06	-0.07	-0.07	-0.11	-0.63	-0.24
SD	0.24	0.36	0.46	0.54	1.26	0.85
	Hypnosis Condition					
	ΔAlpha2 TP7	ΔAlpha2 TP8	ΔAlpha2 T5	ΔAlpha2 T6	ΔAlpha2 P3	ΔAlpha2 P4
H-NPDS	-0.26	0.10	-0.01	0.11	-0.07	0.04
SHCS	-0.39*	0.04	-0.29	-0.04	-0.12	-0.06
Hypnotic Depth	-0.31	0.04	-0.21	-0.06	-0.07	-0.02
Pain Expectation	-0.08	-0.08	-0.25	-0.13	-0.20	-0.12
H-Involunt. in PA	-0.52†	0.14	-0.24	0.09	-0.13	0.03
Mean	-0.45	-0.08	-0.19	-0.13	-0.21	-0.13
SD	1.06	0.26	0.63	0.41	0.70	0.56

* p < 0.05; • p < 0.01; † p < 0.001; False Discovery Rate correction; N = 56 women

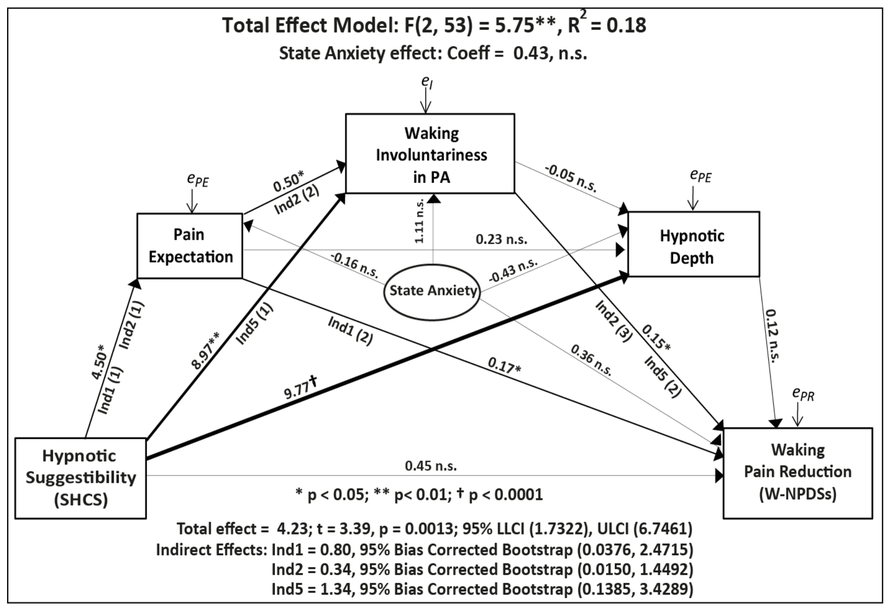

Figure 2. Schematic panel of the serial multiple mediator model linking hypnotic suggestibility to pain reduction.

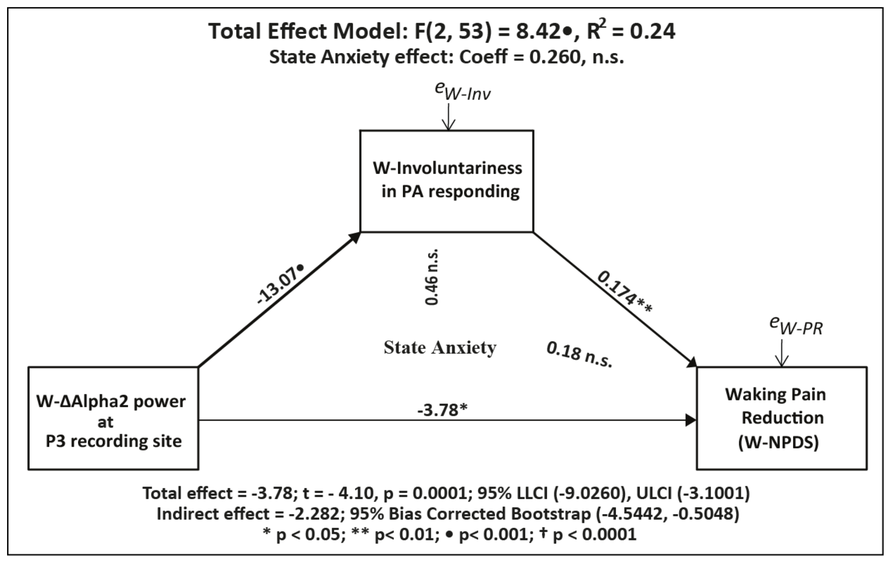

Figure 3. Simple mediator model linking the enhanced alpha2 power at P3 lead to pain reduction.

Conclusion

The present findings obtained in waking state suggest that (1) hypnotic suggestibility causes waking hypoalgesia through the serial mediators of pain expectation and involuntariness in PA responding (**Figure 2**). These significant associations indicate that the increase of involuntariness with the degree of PA responding is not peculiar of hypnosis condition alone, but it is rather a basic process operating in waking condition in conjunction with the placebo effect. (2) enhanced alpha2 power may serve as a direct-objective and indirect measure, through the mediation of involuntariness, of the subjective reduction of tonic pain (**Figure 3**). We believe that the lacking relations found during hypnosis can be due to the fact that, although the placebo effect and hypnosis have in common a process of automaticity, at least to some extent, they also reflect different processes of top-down regulation. This last observation is aligned with our previously reported pain-hypnosis ERP findings (De Pascalis et al, 2015). In sum, the present findings, at least at behavioral level, indicate that both in waking and hypnosis conditions, the variability in placebo analgesia responsiveness is captured by variability in the involuntariness of PA responding.

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