Response Generalization of Placebo Hypoalgesia and Nocebo Hyperalgesia Induced by Verbal Suggestions

Introduction: Placebo and nocebo effects are psychophysiological phenomena that have attracted the attention of researchers for decades due to their ability to modulate pain perception. Numerous studies have shown that these mechanisms are based on learning processes such as verbal suggestion, classical conditioning, and operant conditioning. One of the key components of these processes is generalization, understood as the transfer of a learned response beyond the original learning conditions. Previous research has focused primarily on stimulus generalization—i.e., transferring responses to new but similar stimuli. Much less attention has been paid to response generalization, involving the transfer of placebo or nocebo effects between different somatic symptoms. Therefore, this study was based on two interrelated experiments. In the first phase, a novel experimental model was developed and validated to simultaneously elicit two symptoms—pain and paresthesia (Experiment I). In the next step, using this model, the main study (Experiment II) was conducted to determine whether a placebo and/or nocebo effect, induced through verbal suggestion, could generalize from one symptom (pain) to another (paresthesia).

Materials and Methods: In Experiment I, 40 healthy volunteers aged 18–35 participated. Pain and paresthesia were induced using mechanical pressure stimuli generated by a computer-controlled blood pressure cuff. Stimulation parameters were randomly selected from three pressure levels (100, 150, 200 mmHg) and three durations (90, 120, 150 s). Participants rated the intensity of experienced symptoms in real time using a computerized visual analogue scale (CoVAS), controlled manually via sliders. After each stimulus, an additional retrospective rating was provided using a traditional VAS displayed on a computer screen.

In Experiment II, 90 healthy participants within the same age range (18–35 years) were randomly assigned to one of three groups: placebo (n = 30), nocebo (n = 30), or control (n = 30). In both parts of the experiment, separated by a 15-minute break, the same pressure stimulus was applied: 250 mmHg for 120 seconds. Pain and paresthesia were assessed in real time using the CoVAS scale. Participants in the placebo group received a verbal suggestion indicating a reduction in stimulus intensity in the second session, and as a result, a reduced sensation of pain. The nocebo group received the opposite suggestion—indicating an increase in stimulus intensity and therefore, a symptom severity. The control group was informed that stimulation parameters would remain unchanged. In both experiments, skin conductance response (SCR) was recorded as an objective marker of physiological arousal.

Results: Experiment I**:** General Linear Model (GLM) analysis revealed significant differences in paresthesia for all stimulus durations ($p < 0.01$), but not for pressure intensity—paresthesia symptoms did not increase between 150 and 200 mmHg ($p > 0.05$). In contrast, pain intensity differed significantly across all pressure levels ($p < 0.05$), but not across durations—no significant increases in pain were observed between 90 and 120 seconds or between 120 and 150 seconds ($p > 0.05$). No interaction effects were found for either symptom. Skin conductance response(SCR) analysis did not reveal any significant main effects or interactions. Intraclass correlation coefficients (ICC) indicated moderate to good reliability for pain and paresthesia induction across different durations and intensities (ICC: 0.52 – 0.90), while SCR showed weak to moderate reliability (ICC: 0.21 – 0.73).

Experiment II**:** Repeated measures ANOVA revealed significant interaction effects for the "group × phase" factor in both pain ($p < 0.05$) and paresthesia ($p < 0.05$), suggesting that symptom changes varied by experimental group. For SCR, only a significant main effect of phase was observed ($p < 0.01$), with no interaction. Paired t-tests showed a significant increase in pain ($p < 0.001$, Cohen's $d = 0.88$) and paresthesia ($p < 0.01$, $d = 0.62$) in the nocebo group.

The control group also showed a significant increase in pain ($p < 0.05$, $d = 0.38$), while no significant changes were observed in the placebo group. For SCR, only the nocebo group exhibited a significant increase ($p < 0.05$, $d = 0.47$), but between-group differences were not significant. Independent t-tests (Welch's variant), corrected for multiple comparisons using FDR, showed that increases in pain and paresthesia were significantly greater in the nocebo group compared to both the placebo group ($p_{FDR} < 0.05$ for pain; $p_{FDR} = 0.01$ for paresthesia) and the control group ($p_{FDR} < 0.05$ for both symptoms). No significant differences were found between the placebo and control groups. For SCR, no significant differences between groups were observed.

Conclusion: In the first experiment, a novel experimental model was developed and empirically validated to simultaneously induce two distinct symptoms: pain and paresthesia. The use of pressure stimuli with varying parameters enabled detailed characterization of the relationship between stimulus properties and symptom intensity. Results showed that pain was significantly affected by pressure intensity but not by duration, whereas paresthesia followed an opposite pattern—increasing with longer durations but not with higher intensities. Both symptoms showed good repeatability and moderate to high measurement reliability. In the second experiment, using the developed model, the impact of verbal suggestion on symptom perception and the potential for response generalization of placebo/nocebo effects were investigated. The nocebo suggestion led to a significant increase in perceived pain, which partially generalized to paresthesia. In contrast, the placebo suggestion did not produce the expected effect of hypoalgesia. Despite observable behavioral differences in symptom perception, SCR measures did not reflect significant group differences, suggesting limited sensitivity of this method under the given conditions.

Key words: placebo effect; nocebo effect; response generalization; pain; paresthesia