Nocebo Effects on Cowhage-evoked Itch: A Randomized Controlled Trial of Classical Conditioning and Observational Learning

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To investigate learning processes underlying nocebo effects on itch, this study measured the efficacy of classical conditioning and observational learning for inducing nocebo effects on cowhage-evoked itch and scratching behaviour. A total of 58 healthy female participants were assigned to classical conditioning, observational learning, or sham conditioning groups. In the classical conditioning group, experimenters associated the application of an inert gel with increased itch intensity themselves. In the observational learning group, a video of the conditioning paradigm was shown. Nocebo effects were measured as the difference in itch or scratching between control and nocebo test phase trials, compared between learning and control groups. Compared with sham conditioning, classical conditioning induced a significant nocebo effect on itch, while observational learning did not. No nocebo effect on scratching was detected. These results highlight the role that learning through direct experiences plays in pruritic symptoms. Future research should investigate how a patient's history of unsuccessful treatments shapes treatment outcomes.

Key words: pruritus; learning; nocebo effect; classical conditioning; observational learning; psychodermatology.

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SIGNIFICANCE

Nocebo effects may occur when we learn to expect something bad will happen, such as our itch getting worse, and then, like a "self-fulfilling prophecy", the itch really does get worse because we expected it would. This study investigated 2 different ways in which such nocebo effects can occur in healthy participants: learning expectations through direct experience (classical conditioning) and learning expectations through observation (observational learning). While learning through direct experience led to nocebo effects on itch, there were no indications for observational learning having this effect. This suggests that nocebo effects on itch can arise through first-hand, negative experiences with itch treatments.

Itch is a frequently experienced, unpleasant sensation, which motivates scratching behaviour (1). Itch can be a burdensome symptom for patients, particularly in chronic dermatological conditions (2, 3). Learning processes that promote negative expectancies of treatment may exacerbate symptoms such as itch; such occurrences are known as nocebo effects (4). These changes in the perception of pruritic symptoms are thought to increase burden on patients, prolong illness, and reduce the efficacy of otherwise successful treatments (5, 6).

Nocebo effects on itch can arise through learning processes, such as classical conditioning. Through the repeated pairing of a stimulus (e.g. the application of an inert gel) with another, unconditioned stimulus (e.g. rubbing cowhage into the skin) that naturally evokes a given response (e.g. itch), the conditioned stimulus (gel) alone can come to evoke a similar response (7). Such conditioned responses can be enhanced with verbal suggestions explicating this relationship (8). Although less studied than classical conditioning, observational learning can also induce nocebo effects (9). For example, by observing someone else experiencing increased pain following the application of an inert gel that observers believed was a hyperalgesic, observers experienced similarly increased pain following administration of the same inert gel (10–12). Although these studies demonstrate a role of observational learning in nocebo effects on pain, no studies have investigated observational learning of nocebo effects on itch.

In previous studies of nocebo effects on itch, itch has been induced with histamine (7, 13), mechanical, and electrical stimulation (5, 8). Unlike histamine, cowhage induces itch by acting on Mas-related G-protein coupled receptors (14) and proteinase-activated receptor (PAR) 2 and 4 receptors (15, 16). Notably, there is overexpression of PAR receptors in the chronic dermatological condition atopic dermatitis (AD) (17, 18). Relative to the sensations of electrical or mechanical stimulation, the prickling, burning sensation cowhage evokes may be qualitatively more similar to itch experienced in clinical conditions (19, 20). Therefore, studying these processes with cowhage offers a novel and potentially more clinically relevant model of nocebo effects on itch.

The aim of this study was to elucidate nocebo effects on cowhage-evoked itch with classical conditioning and observational learning of a classical conditioning para-

digm, each with verbal suggestion. A better understanding of how these learning processes contribute to nocebo effects may help in preventing and detecting the learned exacerbation of pruritic symptoms. It was hypothesized that classical conditioning with verbal suggestion would induce nocebo effects on cowhage-evoked itch, and secondarily hypothesized that observational learning with verbal suggestion would induce nocebo effects on itch. Furthermore, this study explored whether nocebo effects on scratching behaviour were also induced, and whether the psychological factors anxiety, stress, empathy, positive and negative affect, and participants' understanding of the experiment, correlated with nocebo effects on itch.

MATERIALS AND METHODS

Ethics

The study was approved by the Psychology Research Ethics Committee, Leiden University (CEP-19-0225/128), and was preregistered in the Netherlands Trial Register (NL7696). The study was conducted in accordance with the Declaration of Helsinki (21).

Participants

Participants were tested in March–May 2019 ($n=66$, English-speaking, females, age range 17–35 years). Exclusion criteria were: current physical or mental illness; colour blindness; current use of medication; current injuries on hands, wrists, or arms; and cowhage insensitivity. The sample size was derived from a power analysis based on Bartels et al. (8). These authors compared classical conditioning with verbal suggestion vs sham conditioning to induce nocebo effects on electrical itch, yielding an effect size of $\eta_g^2 = 0.124$. The number of participants needed per group to detect such an effect ($\alpha = 0.05$, power = 0.95) using a 2×2 mixed analysis of variance (ANOVA) was 16 subjects. Given the novelty of conditioning with cowhage, anticipated dropouts, and possible non-responders to cowhage (individuals who reported no itch after 2 attempts to apply cowhage), 22 participants were recruited per group.

Design

A 3-group design was used to compare nocebo effects induced with: (*i*) classical conditioning, (*ii*) observational learning, and (*iii*) sham conditioning, each with verbal suggestion, between subjects. Nocebo effects were measured within participants as the difference in self-reported itch, or frequency and duration of scratching, during nocebo and control test trials, and compared between learning groups and the control group.

Itch-evoking stimuli

Itch was evoked with cowhage spicules (*Mucina pruriens*). Cowhage evokes mild to moderate itching, which lasts for several minutes, when rubbed into the skin (22). Cowhage spicules were counted using a stereomicroscope with 20× magnification (Bressler, Rhede, Germany). Low-intensity itch was evoked with 20 active spicules and 20 inactive spicules (low dose). Spicules were rendered inactive by autoclaving in a pressure cooker at 120° C for 1 h. Higher intensity itch was evoked with 40 active spicules (high dose).

For each itch stimulus, the experimenter began by telling the participant which gel would be used. The experimenter then acted as though a small amount of gel was applied to a Q-tip and rubbed the Q-tip on 1 of 6 squares on the participant's arms, demarcated with medical tape. No gel was actually applied, and the Q-tip had been soaked in 70% alcohol, so that it felt as though a substance was applied. Subsequently, the second experimenter entered the room, applied the cowhage, and rubbed the spicules into the participant's skin for 45 s. Once the participant indicated that she felt itch, she rated her itch every 15 s for 3 min, yielding 12 ratings per trial. Subsequently, the experimenter removed the cowhage using medical tape. A 5-min break followed, to allow itch sensations to diminish, while the participant was allowed to read a magazine on a neutral topic. If, at the end of this break, the participant's itch rating was 10 or higher (numerical rating scale (NRS) 0–100), the break would be extended in 2-min increments until the itch had diminished below a rating of 10, to a maximum of 10 min extension, though this situation never occurred.

Nocebo and control stimuli

Two opaque white plastic bottles with large blue or yellow labels, purportedly containing either a medical itch-increasing gel or an inert control gel were used as the nocebo and control stimuli. The colours of the nocebo and control labels were counterbalanced across participants.

Measures

Itch. Participants' self-reported itch intensity was measured on a 0–100 NRS. A rating of 0 indicated "no itch at all", and a rating of 100 indicated "the worst itch imaginable". Verbal itch ratings given by the participant were recorded by the experimenter.

Scratching. Participants were informed before each cowhage trial that they could scratch around the square in which cowhage was applied, but not directly on the site. Frequency and duration of scratching behaviour was coded for each learning and test phase trial using video recordings of each consenting participant's laboratory visit. The videos were coded by 2 observers (1st and 4th authors) using The Observer XT 14 software (Noldus Information Technology, 2019, Wageningen, The Netherlands). Inter-rater reliability was assessed on 10 videos coded by both observers, resulting in 92.5% agreement on frequency of scratching behaviours, and 89.7% on scratching duration.

Questionnaires. Questionnaires were used to assess state anxiety (Spielberger State Trait Anxiety Index; STAI (23)), trait empathy (Brief Interpersonal Reactivity Index; B-IRI (24)), affect (Positive and Negative Affect Schedule; PANAS (25)), and stress (Perceived Stress Scale; PSS (26)). Participants in the observational learning group completed a survey after the observational learning manipulation, and all participants answered 3 manipulation check questions regarding their understanding of the experiment.

Procedure

Pre-experiment. Potential participants were recruited through online advertisements and flyers. The study was advertised as an investigation of individual differences in sensitivity to itch. After registering, eligibility was checked with an online survey. Eligible participants completed an additional online survey containing the B-IRI and PSS. Informed consent for pre-experimental procedures was given electronically.

Experimental procedure. Participants were tested in a laboratory at Leiden University, the Netherlands. One of 7 trained student experimenters led the procedures in the laboratory, while a second experimenter (the first author or a student) prepared the cowhage doses in an adjacent observation room. All participants gave informed consent to participate. Eligibility criteria were re-checked by the experimenter, and participants completed a survey (STAI, PANAS, and demographics). Concurrently, the second experimen-

ter opened a sealed, opaque envelope containing the participant's random group allocation. The allocation sequence was generated by an independent researcher using a random number generator function with blocks of 12 (ratio 1:1:1). Given the different procedures for each group, experimenters were not blind to the participant's group allocation.

Classical conditioning. Participants in the classical conditioning group were told that the study aimed to investigate how their response to cowhage-evoked itch was affected by a gel known to increase itch, and how psychological factors influenced this effect. Participants were informed that they would complete 3 trials of applying the active gel followed by cowhage (nocebo trials), and 3 trials with an inert control gel followed by cowhage (control trials). While giving these instructions, the experimenter gave the following verbal suggestion, "The control gel will not affect the itch that you feel. The active gel will make your itch worse." While this verbal suggestion was only made once, the gels were referred to as the active or control gel before each trial. The 4 learning trials were always conducted in the order shown in **Fig. 1**; first with 2 trials on upper and lower squares of the right arm, followed by the upper and lower squares of the left arm. The order of the 2 test trials (control and nocebo) was pseudorandomized, while the location was fixed (first the left arm, second the right arm). During the learning phase, the control trials used the low dose of cowhage, while the nocebo trials used the high dose of cowhage. During the test phase, both trials used low doses of cowhage.

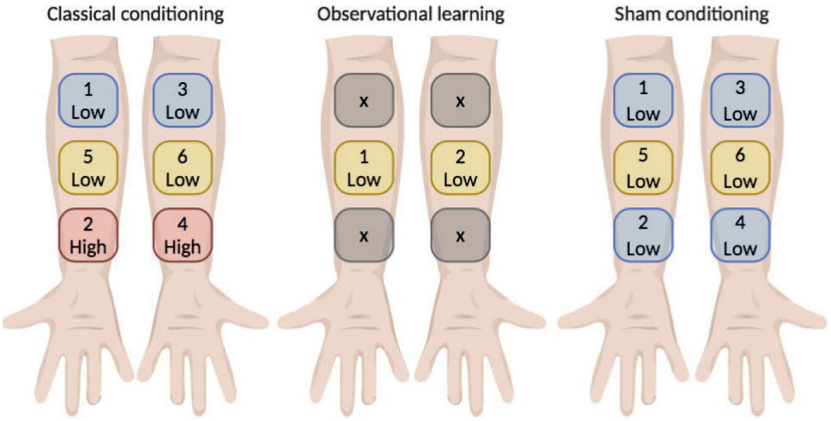

Fig. 1. Order and location of trials for each of the 3 groups. The numbers indicate the order of trials, and the terms "low" and "high" indicate the dose of cowhage. *Blue squares* denote control learning trials, *red squares* denote nocebo learning trials, and *yellow squares* denote test phase trials. *Grey squares* in the observational learning group indicate itch trials that were observed through a video of a model participant.

Observational learning. Participants in the observational learning group were told that to standardize how the experiment was explained, they would be shown a video depicting the procedure instead of having it explained to them. The video depicted all 4 learning trials of the classical conditioning procedures. A model female participant was seated in the same position as the participant viewing the video, and an experimenter could be heard explaining the procedure, beginning with the verbal suggestion. The model participant reported a mean itch rating of 30 for control trials, and 60 for nocebo trials. Participants took 5-min breaks between video trials. Following the video, participants completed a questionnaire on the video, then underwent the same test phase as participants in the other 2 groups.

Sham conditioning. The procedure for the sham conditioning group was identical to classical conditioning, with the exceptions of the verbal suggestion and the cowhage doses used in the learning trials. Instead, participants were told, "The gels are expected to have the same effect on itch, so you should feel no difference in itch between the 2 gels." The low dose of cowhage was used for all trials.

Post-experiment. Participants were asked 3 manipulation check questions regarding their understanding of the experiment, and were subsequently debriefed. The experiment lasted 90 min. Participants received €15 or course credits in compensation. The full study protocol will be available online (https://www.trialregister.nl/trial/7696).

Statistical analyses

Data were analysed with SPSS (IBM, version 25, Armonk, NY, USA). Normality, homogeneity of error variance, and statistical outliers were checked for all data. To test the primary hypothesis, the interaction effect was examined in a 2×2 (group: classical vs sham conditioning) × (trial type: control vs nocebo) mixed analysis of variance (ANOVA), with the mean itch rating per trial as the dependent variable. Effect sizes are reported as generalized eta-squared (27). *Post hoc* comparisons of trial types within each group were carried out with paired samples *t*-tests.

To test the secondary hypothesis, a similar 2 × 2 mixed-model ANOVA was conducted, in which the between-subjects factor of group consisted of the observational learning and sham conditioning groups.

To test the exploratory hypothesis that classical conditioning and observational learning would induce nocebo effects on scratching behaviour, 2×2 mixed-model ANOVAs were conducted separately for total frequency and duration of scratching behaviour. As before, these ANOVAs compared group by trial type interactions between either classical conditioning or observational learning groups and the sham conditioning group.

Pearson's correlations were used to measure the correlations between nocebo effects and questionnaire data.

RESULTS

Demographics

Of the 66 participants, 5 were excluded during testing; 4 due to cowhage insensitivity detected during the first learning trial, and one who identified the exact aim of the experiment during a manipulation check at the end of the experiment. Data from these participants were not

Table I. Demographics of study participants

	Classical conditioning *n* = 19	Observational learning *n* = 21	Sham conditioning *n* = 18
Age, years, mean (SD)	21.8 (2.4)	22.2 (2.4)	21.7 (2.4)
Range	19–26	17–31	19–26
Education *n* (%)			
Did not complete secondary education	1 (5)	1 (5)	0 (0)
Secondary education	18 (95)	20 (95)	18 (100)

Sample size, age, and education level data for each group of participants included in analysis. Participants were asked to identify the highest level of education they had completed. Secondary education is considered as having completed a secondary/high-school diploma.
SD: standard deviation.

included in any analyses. Participants' demographics are shown in **Table I**.

Nocebo effects

Assumptions and outliers. Based on difference in itch ratings between control and nocebo test trials, 3 statistical outliers (z >2) with exceptionally large differences between trials were excluded from all analyses. One exclusion from classical conditioning (z =–2.29), one from observational learning (z =–2.58), and one from sham conditioning (z =–2.62). This yielded a final sample of 58 participants. Normality and homogeneity of variance are reported in Appendix S1[1].

Classical conditioning. A 2×2 mixed ANOVA detected a trial type by group (classical vs sham conditioning) interaction on itch ratings [$F(1,35)=4.76$, $p=0.036$, $\eta_g^2=0.01$] (**Fig. 2**). The interaction was driven by participants in the classical conditioning group who rated their itch significantly higher during the nocebo trial (mean ± standard deviation (SD) 31.1 ± 20.1, 95% confidence interval (95% CI) 21.4–40.8) than during the control trial (21.1 ± 19.1, 95% CI 15–29.8; $t=2.69$, $p=0.015$), whereas participants in the sham conditioning group had nearly the same reported itch intensity for the nocebo trial (22.4 ± 15.4, 95% CI 11.9–31) and control trial (20.9 ± 19, 95% CI 11.5–30.4; $t=0.05$, $p=0.965$). Without excluding outliers, the interaction was not significant [$F(1,37)=3.34$, $p=0.076$, $\eta_g^2<0.01$].

Observational learning. A 2×2 mixed ANOVA detected no trial type by group (observational learning vs sham conditioning) interaction [$F(1,37)=2.13$, $p=0.15$, $\eta_g^2<0.01$] (Fig. 2). The pattern of results did not change when outliers were included [$F(1,39)=1.14$, $p=0.236$, $\eta_g^2<0.01$].

Scratching. Two 2×2 mixed ANOVAs detected no trial by group (classical vs sham conditioning) interaction on scratching frequency [$F(1,35)=0.94$, $p=0.336$, $\eta_g^2=<0.01$] or duration [$F(1,35)=1.35$, $p=0.253$, $\eta_g^2=0.01$]. Similarly, 2×2 mixed ANOVAs detected no trial by group (observational learning vs sham conditioning) interaction on scratching frequency [$F(1,37)=0.19$, $p=0.664$, $\eta_g^2=0.01$] or duration [$F(1,37)=0.09$, $p=0.761$, $\eta_g^2=0.01$]. Frequency and duration data by group and trial type are reported in Table SI[1].

Questionnaire and learning data. No significant correlations between nocebo effects and the questionnaires, including the manipulation check items were detected. These results, and learning phase data, are reported in Appendix S1[1], Table SII[1], Figs S1[1] and S2[1].

DISCUSSION

This study found that nocebo effects on cowhage-evoked itch can be induced through classical conditioning with verbal suggestion, but did not find evidence for nocebo effects induced through observational learning with verbal suggestion. Neither learning process induced nocebo effects on scratching behaviour. No correlations with psychological factors were detected.

This study replicated and extended earlier findings demonstrating that conditioning with verbal suggestion induces nocebo effects on itch (5, 7, 8). These findings indicate that learning through direct experience can have a small exacerbating effect on perceived itch symptoms. The mean magnitude of the nocebo effect following classical conditioning with verbal suggestion was approximately 10 points on a 0–100 itch scale, indicating that nocebo effects can yield small, but perceptible, increases in itch for healthy individuals. While previous studies used a large number of pruritic trials during conditioning (5, 7, 8, 28), the current study used considerably fewer itch stimuli (e.g. one-fifth of the itch stimuli relative to Bartels et al., 2014; (8)), lasting twice as long, in combination with verbal suggestion. This suggests that nocebo

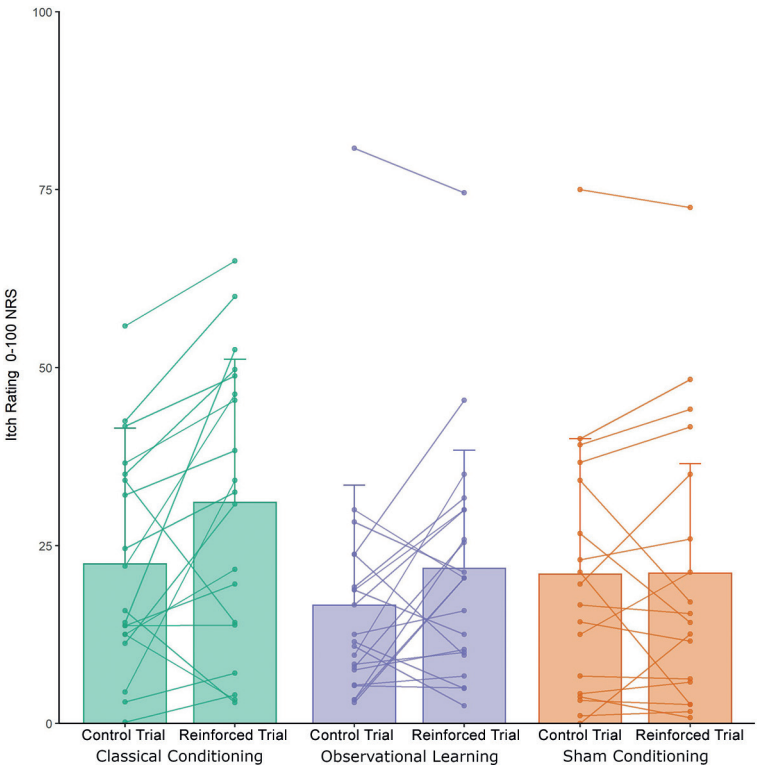

Fig. 2. Mean itch ratings during the control and nocebo test trials by group, excluding outliers ($n=58$), with individual participant data plotted on top of group means ± standard deviation (SD). Lines connect individual participants' data from control to nocebo trials. NRS: numerical rating scale.

[1]https://doi.org/10.2340/00015555-3723

effects may form after only a few experiences with longer pruritic stimuli and associated cues.

Observational learning did not yield a significant nocebo effect on itch, in contrast to research on nocebo effects on pain (10–12). For comparability of the groups, the video was the same length as the conditioning paradigm. However, the length of the video may have resulted in participants losing interest and insufficiently learning the associations between the nocebo stimulus and increased itch, since observing a video may be less engaging than experiencing conditioning first hand. Previous studies that investigated observationally induced nocebo effects on pain used shorter videos (10, 12) without comparing the effect with classical conditioning. Future research on observationally learned nocebo effects on itch should similarly consider a shorter manipulation. This could increase the ecological validity of the learning process, in which observationally learned associations develop over numerous, brief observations instead of fewer, longer observations. Alternatively, observational learning may be an effective process for inducing nocebo effects on pain, but not on itch, at least in healthy individuals. In healthy participants the threat from pain may be seen as greater than that of itch, and therefore itch may not attract the same attention necessary for observational learning as pain does (29). Finally, as the sample size was calculated based on research assessing an effect for live classical conditioning with verbal suggestion, future studies with sufficient statistical power to test for an effect of observational learning are needed to assess the role it may play in nocebo effects on itch.

No nocebo effects on scratching frequency or duration were detected. Although nocebo effects can increase the subjective experience of itch, there does not appear to be a corresponding change in behaviour. Nocebo effects on histamine-evoked itch have been found to correlate with larger wheal and flare reactions to histamine, indicating that the nocebo effects may extend beyond subjective experience to physiological processes (30), but further research is needed to determine whether these effects impact behaviour. In the present study, participants were prevented from scratching directly on the sites where cowhage was applied, in order to avoid disrupting the itch-evoking manipulation (e.g. spreading or removing cowhage spicules from where they were applied); however, this may have interfered with potential nocebo effects on scratching. Also, although participants were reminded that they could scratch during each itch trial, they may have scratched less in the presence of the experimenter than they would have if they had been alone.

The cowhage used in this study could offer a better model of pruritic symptoms than the pruritogens used in previous nocebo studies (5, 7, 8, 28). While still an acute model of itch, cowhage acts on PAR 2 and 4 pathways, which are thought to play a role in itch experienced by patients with AD (17, 18). Although a single-day experiment in healthy participants does not replicate the prolonged experience of chronic pruritic symptoms, by investigating nocebo effects with cowhage, we can model these effects on the same physiological pathways underlying chronic conditions such as AD.

An important next step for research into nocebo effects on itch would be to establish a better understanding of the psychophysiological differences between healthy individuals and those with chronic pruritic symptoms. While central sensitization posits that patients should respond with heightened sensitivity to itch stimuli (31), a systematic review of studies on this topic did not find evidence to support this theory (32), though more research is warranted. There is some evidence that patients with chronic pruritic conditions are more susceptible to psychophysically induced itch than individuals without such conditions (28, 33, 34) and, ideally, future research should directly compare learned nocebo effects on itch across these 2 populations. Understanding the differences between healthy individuals and patients on psychophysiological mechanisms of itch will aid in assessing the prevalence and severity of nocebo effects on itch in clinical settings, and in tailoring responses to these effects.

To conclude, this study found that classical conditioning with verbal suggestion induced small nocebo effects on itch, but did not find similar evidence for an observational learning manipulation of the same content and length. These results have expanded the current understanding of learning processes underlying nocebo effects on itch in several ways. This study made use of a novel, and more clinically transferrable, model of itch for this field, with the use of cowhage to induce nocebo effects on itch. The study also demonstrated that conditioning can take place with fewer and longer pruritic stimuli than used previously. As nocebo effects on itch may form with as few as one-fifth of the stimuli used previously, their potential negative impact in clinical settings may be more common than previously thought. These and previous findings suggest a need for future research to investigate whether nocebo effects may present in patients experiencing itch. Caused by negative treatment experiences, nocebo effects may increase symptom severity, blunt the success of effective treatments, and thereby contribute to a worse prognosis.

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