Supplementary Material

Antipruritic placebo effects by conditioning H_1-antihistamine

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Abbreviations used in the supplementary material

ANCOVA = Analysis of Covariance

ANOVA = Analysis of Variance

ATS/ERS = American Thoracic Society / European Respiratory Society (Task Force)

BIS/BAS scales = the Behavioural Inhibition System / Behavioural Approach System scales

BPM = Beats per Minute

CS = Conditioned Stimulus

DSM-IV = the Diagnostic and Statistical Manual of Mental Disorders-IV

EPQ-RSS-EN = Eysenck Personality Questionnaire short–extraversion & neuroticism

FEV_1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

GLM = General Linear Model

HADS = the Hospital Anxiety and Depression Scale

HR = Heart Rate

IgE = Immunoglobulin-E

LOT-R = the Life Orientation Test – revised

LUMC = Leiden University Medical Center

MEFV = Maximum Expiratory Flow-Volume curve

NA = Negative Affect

NRS = Numeric Rating Scale

PA = Positive Affect

PANAS = Positive and Negative Affect Schedule

PEF = Peak Expiratory Flow

PSS = Perceived Stress Scale

PSWQ = Penn State Worry Questionnaire

RAND-36 = a multidimensional measure of general health status

RMA = Repeated Measures Analysis

SCL = Skin Conductance Level

SS-10 = Sensitive Scale-10

STAI-S-s = State Trait Anxiety Index – State – short scale

UCS = Unconditioned Stimulus

Supplementary Methods

2. Elaboration on the participant group

Healthy male and female volunteers, aged between 18 and 35 years, were recruited for this study through advertisements at locations of Leiden University, the Leiden University Medical Center (LUMC), the University of Amsterdam, and the University of Delft, and through social media (e.g., Facebook). Inclusion criteria consisted of a good understanding of written and spoken Dutch, and absence of allergic rhinitis or allergic conjunctivitis within the three months prior to enrolment in the study. Participants were excluded in case of any (severe) allergic condition that presented symptoms other than rhinitis or conjunctivitis (e.g., food allergy); sensitivity to levocetirizine diHCl or other substances used in the study; lactose intolerance; somatic morbidity that could interfere with the participant's safety or with the study protocol (e.g., histamine intolerance, asthma); current Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) psychiatric diagnoses; recent (within past 2 months) use of antihistamines, antibiotics, or anti-inflammatory medication; recent vaccinations; and pregnancy. Participants were asked to refrain from consuming heavy meals, caffeine, or smoking 2 hours, exercise 12 hours, and alcohol and drugs 24 hours prior to the sessions. Adherence to these lifestyle guidelines, as well as any significant changes in health status during the course of the study (e.g., illness or other changes in physical health, or occurrences of highly stressful events) were monitored at the start of each session.

4. Elaboration on the conditioning paradigm

The CS was a distinctively-tasting green beverage that has been used as a CS in previous conditioning studies (2-7). The beverage consisted of 150 mL of commercially available strawberry milk, which was coloured green by adding the coloring powders Quinoline Yellow

(E104, 80 mg/L) and Patent Blue V (E131, 20 mg/L) and flavoured with lavender oil (0.6 mL/L)[1]. As unconditioned stimulus (UCS), 5 mg of levocetirizine diHCl was capsuled by the LUMC pharmacy. Identically-looking placebo capsules were also prepared by the pharmacy. Presentation of the CS and UCS or placebo in both the acquisition and evocation sessions was accompanied by a brief instruction that emphasized: 1) that it was important that the beverage and capsule were taken simultaneously, and 2) that the experimenter did not know whether the capsule contained active medication or an inert substance (for the open-label conditioned group, a different instruction was used, see '*5.1. Open-label instructions*').

5. Elaboration on materials and measures

5.1. Open-label instructions

At the start of the acquisition phase, participants in the open-label conditioned group were provided with scripted instructions regarding five points: 1) that part of the effects of anti-allergic medication can be learned through the principle of conditioning, 2) that an example of conditioning is the experiment of Pavlov, in which a dog was taught to respond to the ringing of a bell with salivating, by pairing this sound with food, 3) that this learning paradigm can be utilized for medication use by, for example, pairing medication with a beverage, 4) that these effects may be large, and potentially just as large as the effects of the medication itself, and 5) that effects may be noticed in the evocation phase, for example, as improved performance on the spirometry tests and reduced itch during iontophoresis in the final session. During each session, administration of the beverage and capsule was accompanied by instructions that consisted of a brief repetition of points 1 and 4. In addition, point 5 was briefly repeated at the start of the final session.

[1] Three participants (1 in the open-label conditioned group, 2 in the conditioned-not-evoked group) received a beverage containing 160 mg/L of Quinoline Yellow and 40 mg/L of Patent Blue due to administrative error. Subanalyses of the total sample without these participants indicated no differences in the main results.

5.2. Histamine iontophoresis

Itch was evoked experimentally by transdermal histamine iontophoresis (Chattanooga Group, Hixson, TN, USA) at baseline and during the final evocation session. Histamine iontophoresis has been previously used as a reliable method to induce itch in healthy participants (8-11). An electrode with an active surface of 11.7 cm^2 (Iogel, Iomed, DJO Global, Hannover, Germany) was treated with 2.5 ml of a 0.6% diphosphate histamine solution (prepared in distilled water with propylene glycol and Hypromellose 4000 mPa; equivalent to 1% histamine dihydrochloride). The prepared electrode was placed on the volar side of the non-dominant forearm. A reference electrode was placed on the volar surface of the upper arm. Histamine iontophoresis was conducted for 2.5 minutes with the current level set at 0.4 mA.

5.3. Primary outcome measure: self-reported itch

During iontophoresis, itch was assessed verbally every 30 seconds on a Numeric Rating Scale (NRS) ranging from 0 (*'no itch'*) to 10 (*'worst itch ever experienced'*). Directly following iontophoresis, mean self-reported itch during the test was assessed using the same NRS. Between 1 and 4 minutes after iontophoresis, itch was again assessed every 30 seconds as a follow-up period to the test. Mean self-reported itch during iontophoresis assessed directly following iontophoresis was used as the primary outcome measure, and correlations with other itch measures taken during iontophoresis were calculated in order to validate the reliability of the main outcome measure.

5.4. Secondary outcome measures

5.4.1. Expectations regarding histamine iontophoresis

Participants rated the amount of itch they expected to experience during iontophoresis on the same NRS as used for the itch assessments. Measures of expectations were taken at the start of

both the screening session and the final evocation session. Moreover, participants rated the amount of itch they expected to experience during the final evocation session at the end of the screening session (following the first iontophoresis test). Finally, using the same NRS, participants rated, prior to histamine iontophoresis in the final evocation session, how much itch they remembered experiencing at baseline (screening session), as well as the expected efficacy of the administered capsules (0 *'not effective*', 10 *'very effective'*).

5.4.2. Self-rated skin response

Self-rated skin response was measured using an adjusted version of the Sensitive Scale-10 (SS-10; (12)). This questionnaire assesses a variety of skin symptoms that are either subjectively experienced (e.g., itch, tingling, burning, pain), or visibly rateable (e.g., redness of the skin). Symptoms are rated on a 0 ('zero intensity') to 10 ('intolerable intensity') scale. Total scores are calculated by summing across items. For the purpose of the current study, the timeframe for which the symptoms were rated was tailored to histamine iontophoresis (i.e., *'during the histamine test'*, rather than the original *'during the past three days'*). As a baseline measurement, participants also filled in the original questionnaire. Cronbach's alpha was .58 for the original questionnaire in the current study. For the adjusted SS-10 following histamine iontophoresis at baseline and during evocation, Cronbach's alpha was .88 and .89, respectively.

5.4.3. Clinical skin response

A 1 cm^2 gridded, transparent sheet was used to trace the wheal and flare area in response to histamine iontophoresis. The outer edges of the drawn areas were retraced in ImageJ (13), after which the areas of the wheal and flare response were calculated in cm^2. Skin temperature following iontophoresis was measured using a handheld infrared thermometer (accuracy ±2.0 °C, resolution 0.1 °C, BaseTech, Conrad Electronic Benelux B.V., Hirschau, Germany).

Measurements were taken with the thermometer held approximately 1 cm above the centre of the wheal. A similar measurement was taken on the same area of skin on the opposite arm, to control for individual differences in skin temperature. Increase in skin temperature as a result of iontophoresis was calculated by subtracting temperature of the control area from temperature of the wheal area, with positive values indicating a higher skin temperature increase following iontophoresis.

5.4.4. Spirometry

Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force guidelines on the Standardisation of Lung Function Testing (14). The experimenters were trained in spirometry by certified technicians at the LUMC. Tests were performed using a mounted, non-heated Lilly type pneumotachograph and SentrySuite software package Version 2.7 (Carefusion, Hoechberg, Germany). For FVC and FEV_1, percentages of the predicted scores were calculated using the standard DE#GLI 2012 reference values (15). Tests that did not meet the acceptability and repeatability criteria were excluded from analyses.

5.4.5. Heart rate and skin conductance level

Heart rate (HR; in beats per minute, BPM) and skin conductance level (SCL) were measured during the screening session and during the sessions of the evocation phase. Measurements were taken using an MP150 system and Acqknowledge software, version 4.4 (BIOPAC Systems Inc., Goleta, CA, USA). As has been done previously by our research group (16), the skin was abraded with Nuprep scrub (Weaver and Company, Aurora, CO, USA) in preparation of the HR measurements, after which two disposable electrodes were placed (Ø 38 mm; Kendall 200 Foam Electrode, Covidien, Mansfield, MA, USA) on the sternum and on the participant's

left side below the ribs. An ECG100C amplifier at 100 Hz with a gain of 100, a 0.5-Hz high pass and a 35-Hz low pass filter, and a 50-Hz notch filter measured the electrocardiography signals. The skin was cleaned with water in preparation of the SCL measurements, after which two disposable Ag/AgCl electrodes (Ø 32 mm; DBF3D77, Multi Bio Sensors Inc., El Paso, TX, USA) were placed on the medial phalanges of the index and middle finger of the non-dominant hand. A GSR100C amplifier at 1000 Hz with a gain of 10 μmho/V and a 1.0-Hz low pass filter recorded SCL. Five-minute HR and SCL resting state measurements were taken, once in the screening session, and at various time points during evocation (i.e., prior to, and every 30 minutes post-CS administration). Visual inspection of the data and calculation of mean HR and SCL were done using the Physio Data Toolbox Version 0.1 (17), a standalone MATLAB-based application (MATLAB Release 2016a, The MathWorks, Inc., Natick, MA, USA) that was written at the Faculty of Social and Behavioural Sciences at Leiden University.

5.4.6. Self-rated wellbeing

Self-rated wellbeing was measured throughout the study by means of questionnaires. To measure positive affect (PA) and negative affect (NA), the 20-item Positive and Negative Affect Schedule (PANAS; (18)) was administered. Cronbach's alpha ranged from .88 to .93 for PA in the current study. As the scores for NA were only within the lower range of the scale for all participants, NA data were not analysed. A short 6-item version of the State Trait Anxiety Index – State Anxiety (STAI-S-s; (19)) was administered to assess state anxiety. Cronbach's alpha ranged from .66 to .81. In addition, participants were asked to rate seven psychological states (relaxed, nervous, calm, well, tense, concerned, stressed) on Numeric Rating Scales (NRS) ranging from 0 (*'not at all'*) to 10 (*'very much so'*). The four negative items were recoded and all NRS were summed and divided by seven to calculate a general wellbeing score, for which Cronbach's alpha ranged from .81 to .91.

5.4.7. Taste of the Conditioned Stimulus (CS)

Following each administration of the CS in the acquisition and evocation phase, participants rated the taste of the beverage on a 9-point Likert scale (1 *'very unpleasant'* to 9 *'very pleasant'*). For the conditioned-not-evoked group, the CS was not administered during the evocation phase. Instead, the capsule was administered with water and, to standardise procedures over all groups, participants were asked to rate the taste of the water. The ratings of water during the evocation phase for the conditioned-not-evoked group were not analysed.

5.5. Additional measures: potential predictors of conditioned effects

5.5.1. Atopic constitution and allergy

To assess whether participants were allergic or had a tendency towards allergic or overly sensitive responses (atopic constitution), participants were asked during the screening to indicate whether they had ever experienced any allergic responses to food, animals or pollen. In case of severe allergic responses, e.g., throat swelling, or in case of recent allergic responses, participants were excluded. In addition, blood samples were taken at the LUMC, to assess eosinophil profile and to conduct an allergy test using the blood Immunoglobulin-E (IgE) response to inhalant allergens. Blood samples were treated with a mixture of various aeroallergens (i.e., dust mite, grass pollen, animals, birch, mugwort) and the IgE response was measured and divided into semiquantitative classes to determine sensitization level (20). Data were collected in order to assess – in the event of significant effects of conditioning on the outcome parameters – whether these effects may potentially differentiate between subgroups of participants. Of all participants, 27 (31%) indicated being allergic to either food products or aeroallergens, and 34 (37%) responded positively on the aeroallergen IgE test.

5.5.2. Individual characteristics

Individual characteristics and personality factors were assessed during the screening session. Participants filled in the following questionnaires: a multidimensional measure of general health status, the RAND SF-36 Health Status Inventory (RAND-36 (21)), the Behavioural Inhibition System / Behavioural Approach System scales (BIS/BAS scales (22)), the Eysenck Personality Questionnaire short version – subscales extraversion and neuroticism (EPQ-RSS-EN (23)), the Hospital Anxiety and Depression Scale (HADS (24)), the Life Orientation Test – revised (LOT-R (25)), the Perceived Stress Scale (PSS (26)), and the Penn State Worry Questionnaire (PSWQ (27)). Potential moderating effects of individual characteristics were tested and are described in the supplementary material (see section 7.5.).

6. Elaboration on the general procedure

6.1. Pre-enrolment procedures and additional details on the screening session

Prior to the study, potential participants were briefly screened for the in- and exclusion criteria by telephone, and subsequently, potentially eligible participants were invited to the laboratory for a first (screening) session. An interview was used to further assess whether participants met the inclusion criteria (e.g., presence of any psychological diagnoses according to the DSM-IV criteria). Afterwards, questionnaires assessing individual characteristics and personality factors were filled in, and measurement sets A, B and C were assessed. At the end of the screening session, blood samples were collected at the LUMC to assess eosinophil profile and immunoglobulin-E (IgE) response to aeroallergens for potential subgroup analyses, as well as potential analyses of baseline cytokine levels.

6.2. Acquisition and evocation phase

The acquisition and evocation phases were scheduled within the same 30-minutes time frame in the next two weeks. Within each phase, all sessions started at the same time on three consecutive days. At the start of each session, participants were given an overview of the procedures of that day, and a brief interview was conducted (e.g., to verify adherence to lifestyle guidelines). Within the evocation phase, participants completed several neutral filler tasks (e.g., reading neutral magazines, and filling out Sudoku and word search puzzles) for the purpose of standardising the time that participants had to spend waiting between measurements. At the end of the final evocation session, participants filled out a closing questionnaire, in which they were asked, for example, whether they believed to have received active medication, and were debriefed about the study purpose. Finally, participants were asked to provide a saliva sample in order to test associations between genotype and the conditioned response (the results of which will be described elsewhere), and a second blood sample was taken at the LUMC to potentially assess blood cytokine levels.

7. Elaboration on statistical analysis

7.1. Pre-analyses checks of data and assumptions

Prior to analyses, variables were checked for normal distribution and outliers, and underlying assumptions for each analysis were checked. To detect differences in demographics and baseline measures of the study outcome parameters, χ^2 tests and general linear model (GLM) analyses of variance (ANOVAs) were used. For wellbeing during the acquisition phase, and taste ratings for the CS throughout the study, GLM ANOVAs were also performed.

7.2. Reliability of primary outcome measure

The primary outcome measure of mean self-reported itch at evocation correlated highly with the calculated average of the itch measures taken during histamine iontophoresis at evocation ($r = .96$, $p < .001$), supporting the reliability of the primary outcome measure used for itch.

7.3. Covariates included in the analyses of the primary and secondary outcomes

All GLM analyses of covariance (ANCOVAs) conducted for expected itch, self-reported mean itch, and the self-rated and clinical skin response were controlled for baseline values (screening session). Expected itch was assessed twice during the screening session: once prior to baseline histamine iontophoresis, and once following baseline iontophoresis (as a measure assessing the amount of itch participants expected to experience during the final evocation session). The latter was included as a covariate in the ANCOVA. For remembered itch and expected efficacy of the capsules, no covariates were included. For the clinical skin response measures of wheal and flare area an additional covariate was included, which consisted of the amount of time between the end of iontophoresis and the drawing of the affected skin areas onto the transparent sheet, in order to control for changes in skin response over time.

7.4. Missing data

Due to technical issues with the equipment for histamine iontophoresis, data of one participant was excluded for the analyses of outcome parameters related to histamine iontophoresis (i.e., expected itch, measurement set C). Due to technical issues and the occurrence of artefacts (e.g., a significant number of extra systoles in HR data), HR and SCL data were not reliable for 4 participants. Subsequently, these participants were excluded from the analyses. For spirometry, only data of participants who performed well on all MEFV curves assessed during evocation (i.e., all 10 tests taken during evocation meeting the ATS/ERS criteria for acceptability and

repeatability, to prevent that the group composition changed for each time point in the study) were included in subsequent analyses, resulting in loss of data of 45 participants. Since conditioning only marginally influenced the primary outcome of itch, no further subgroup analyses based on allergic constitution were conducted, nor were the blood samples analysed for cytokine levels.

7.5. Testing the moderating role of individual characteristics and personality in conditioning the effects of antihistamines for itch

To assess whether individual characteristics would influence conditioning effects on the main outcome of self-reported itch during iontophoresis, controlled for baseline, moderation analyses were conducted according to the Preacher and Hayes moderation regression method PROCESS 3.3. (28). For each individual characteristic (predictor of the conditioned response), a separate moderation model was tested two-sided with an alpha level of .05. Analyses were first conducted for the combined conditioned versus the combined control groups, and then repeated to assess effects for the separate four groups. Bootstrap was set at 5000 samples in PROCESS, and conditional effects were probed at -1SD, the mean, and +1SD. Prior to analyses, group differences in individual characteristics were assessed by one-way ANOVA, and the assumptions of regression were checked. In addition, the predictors were centered, and the group variables were dummy coded prior to moderation analyses (with the non-conditioned control group serving as the reference group). For some predictors (i.e., the RAND-36, the EPQ-RSS-EN, and the HADS subscales), there was very low variance in scores between individuals, and scores were non-normally distributed. For these factors, moderation analyses were not conducted.

Supplementary Results

1. Group differences on individual characteristics and personality

No significant differences between the combined conditioned groups and the combined control groups were found for individual characteristics (all $p>.13$), with the exception of optimism (LOT-R; $F(1,89)=6.07$, $p=.016$). Participants in the conditioned groups scored higher on optimism ($M=18.33\pm2.72$) compared to the control groups ($M=16.93\pm2.67$). Repetition of these analyses for the separate groups showed that factors did not significantly differ between groups ($p\geq.072$). An overview of individual characteristics of the study sample is provided in **Supplementary Table S6.**

2. Moderating role of individual characteristics and personality in conditioning the effects of antihistamine for itch: the combined conditioned and combined control groups.

No significant moderation of the effect of the combined conditioned and the combined control groups on mean itch in response to iontophoresis during evocation was found for optimism, perceived stress, worrying, behavioural activation scales (BAS) drive, fun seeking, and reward responsiveness, or behavioural inhibition scale (BIS) (all group x factor interactions: $p\geq.053$; see **Supplementary Table S7**).

3. Moderating role of individual characteristics and personality in conditioning the effects of antihistamines for itch: separate groups

Optimism was found to moderate the effects of closed-label conditioning on mean itch in response to iontophoresis during evocation, compared to the other groups (closed-label conditioning dummy variable x optimism interaction: $p=.021$; see **Supplementary Table S8**). Higher levels of optimism were related to lower levels of mean itch in the closed-label

conditioned group, compared to the other groups (see **Supplementary Figure S2**). However, post-hoc conditional effects of group at various levels of optimism were not significant ($p \geq .12$). For the other dummy group factors, no effects were found (all $p_{interaction} \geq .29$).

BAS reward responsiveness was found to significantly moderate the effect of the conditioned-not-evoked group on mean itch in response to iontophoresis during evocation, compared to the other groups (conditioned-not-evoked dummy variable x BAS reward responsiveness: $p=.020$). Higher levels of reward responsiveness were significantly associated with higher levels of mean itch in the conditioned-not-evoked group, compared to other groups (conditional effect at +1 SD of BAS reward responsiveness: t=2.18, $p=.032$; see **Supplementary Figure S3**). For the other dummy group factors, no effects were found (all $p_{interaction} \geq .087$). Finally, group effects were not significantly moderated by worrying, perceived stress, behavioural activation scales (BAS) drive and fun seeking, or behavioural inhibition scale (BIS) (all group x factor interactions: $p \geq .077$; see **Supplementary Table S8**).

Concluding note on the moderating role of individual characteristics and personality in conditioning the effects of antihistamine for itch

Some evidence was found for a moderating role for optimism in the closed-label conditioned group compared to others, however, post-hoc conditional effects at various levels of optimism were not significant, illustrating that such an effect may be limited. These results need to be interpreted very cautiously, especially given that the groups differed in optimism at baseline. Finally, a potential moderating effect of BAS reward responsiveness within one of the control groups was shown, with higher reward responsiveness being related to higher itch compared to other groups. This moderation is likely not related to the conditioning procedure, as this moderation also encompassed differences compared to the other control group.

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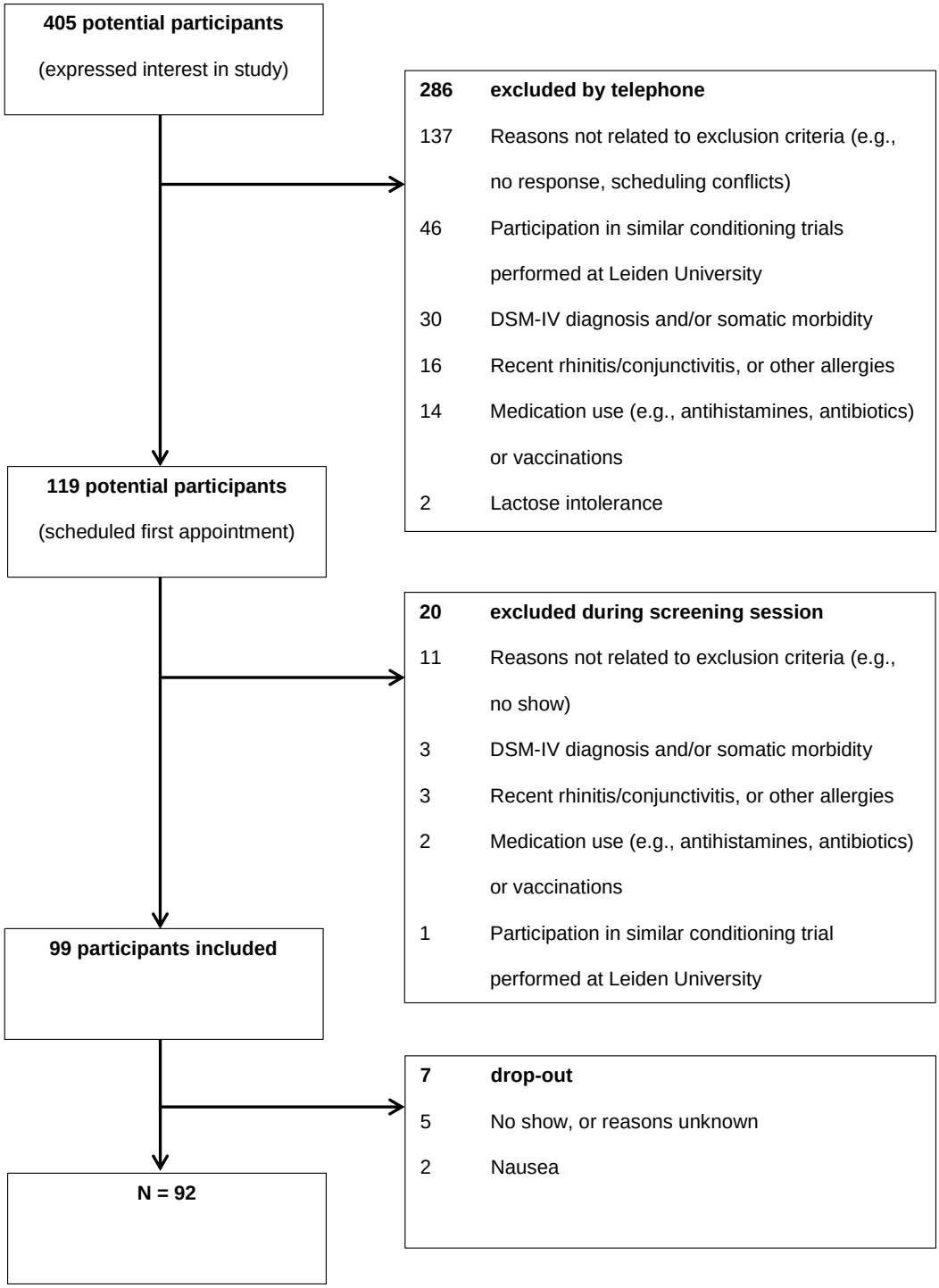
Supplementary Material

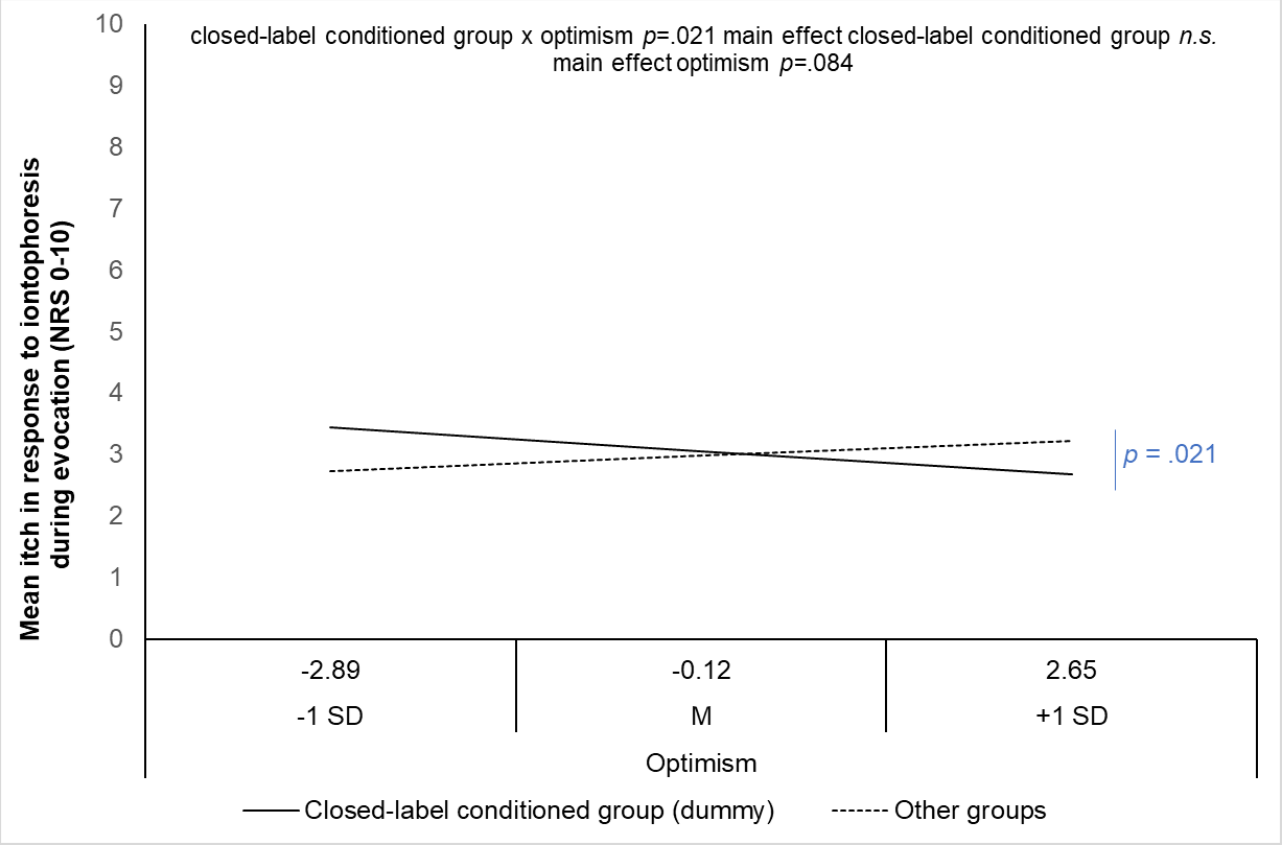
Tables and Figures

Supplementary figures

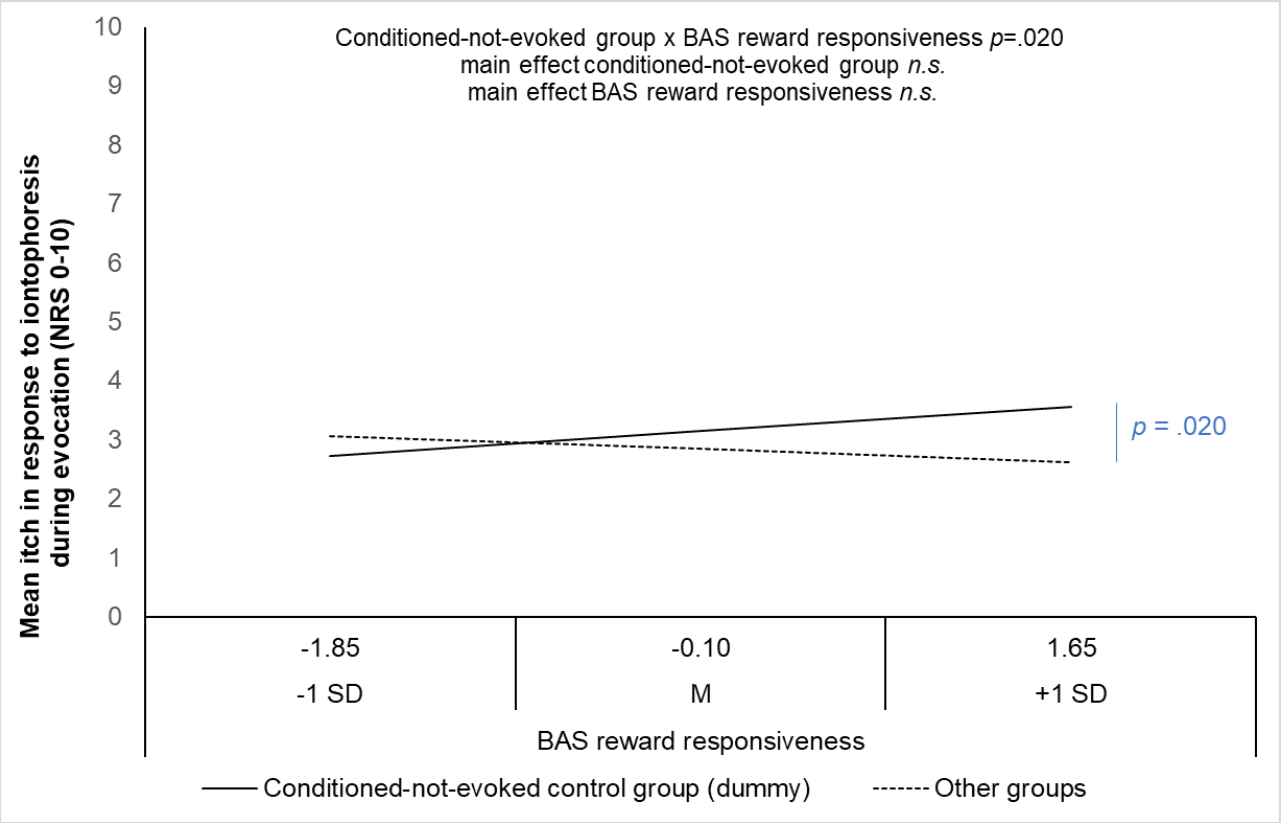
Supplementary Figure S1. In- and exclusion of participants according to protocol criteria and drop-out specifications.



Supplementary Figure S2. Conditional effect of the closed-label conditioned group versus other groups on mean itch during iontophoresis in the evocation phase, controlled for itch during baseline, moderated by optimism.



Supplementary Figure S3. Conditional effect of the conditioned-not-evoked control group versus other groups on mean itch during iontophoresis in the evocation phase, controlled for itch during baseline, moderated by behavioural activation scale (BAS) subscale reward responsiveness.



Supplementary Table S1. Analyses of (co)variance results, means, and standard deviations for the separate groups comparisons

	Open-label conditioned group (n=23)	Closed-label conditioned group (n=23)	Conditioned-not-evoked control group (n=23)	Non-conditioned control group (n=22)	ANCOVA results: effects of group on outcome parameter	
					p	$\eta^2_{partial}$
Demographic factors						
Age [A]	21.87 ± 2.93	23.30 ± 2.96	21.30 ± 1.52	21.59 ± 2.09	.10	
Body Mass Index [B]	23.09 ± 3.25	23.98 ± 3.34	22.99 ± 2.68	22.80 ± 3.97	.64	
Sex [male]: n(%)	3 (13.0)	6 (26.1)	3 (13.0)	3 (13.6)	.56	
Ethnicity [Caucasian]: n(%) [C]	20 (90.9)	21 (95.5)	21 (100.0)	20 (90.9)	.64	
Allergy – anamnesis [yes]: n(%)	6 (26.1)	8 (34.8)	7 (30.4)	7 (31.8)	.94	
Allergy – IgE response [positive]: n(%) [D]	7 (30.4)	9 (39.1)	9 (42.9)	9 (40.9)	.84	
Eosinophilic profile [within normal range]: n(%)	23 (100.0)	22 (95.7)	20 (87.0)	22 (100.0)	.44	
History of antihistamine use [E]	6 (26.1)	6 (26.1)	5 (21.7)	3 (13.6)	.72	
Pre-conditioning histamine iontophoresis (baseline)						
Process measure						
Expected itch pre-iontophoresis	4.57 ± 2.12	3.96 ± 2.01	4.78 ± 1.81	3.54 ± 2.11	.16	.06
Expected itch post-iontophoresis	3.59 ± 1.77	3.99 ± 1.98	4.10 ± 1.78	3.73 ± 2.11	.79	.01
Primary outcome measure						
Mean self-reported itch	3.43 ± 1.82	3.88 ± 2.07	3.62 ± 1.43	3.15 ± 1.87	.58	.02
Secondary outcome measures						
Subjective skin response	22.70 ± 13.04	25.68 ± 15.45	25.35 ± 12.21	23.85 ± 11.58	.86	.01
Wheal area (cm^2) [F]	12.77 ± 2.68	11.90 ± 3.39	10.47 ± 3.83	10.79 ± 3.32	.08	.07
Flare area (cm^2) [F]	48.12 ± 12.34	47.84 ± 12.85	44.66 ± 11.81	49.24 ± 8.91	.63	.02
Change in skin temperature (°C) [G]	1.39 ± 1.44	1.92 ± 1.69	1.36 ± 2.05	1.92 ± 1.69	.50	.03
Post-conditioning histamine iontophoresis (evocation)						
Process measure						
Expected itch [H]	3.21 ± 2.15	4.37 ± 2.24	4.56 ± 1.59	3.94 ± 1.82	.037	.09
Remembered itch from baseline	3.80 ± 2.07	4.11 ± 2.21	3.96 ± 1.85	3.84 ± 2.18	.96	< .01
Expected medication efficacy	5.27 ± 2.29	3.94 ± 2.23	3.81 ± 2.48	3.81 ± 2.37	.11	.07

Primary outcome measure					
Mean self-reported itch [H]	2.50 ± 1.59	3.27 ± 2.24	3.32 ± 1.40	2.70 ± 1.66	.23	.05
Secondary outcome measures					
Subjective skin response	22.58 ± 13.16	25.04 ± 15.52	27.28 ± 11.96	23.41 ± 10.62	.66	.02
Wheal area (cm^2) [I]	11.05 ± 2.94	11.00 ± 3.30	9.46 ± 3.35	10.56 ± 3.46	.61	.02
Flare area (cm^2) [I]	46.03 ± 13.23	44.56 ± 12.66	44.81 ± 11.01	45.84 ± 13.54	.74	.02
Change in skin temperature (°C) [G H]	1.46 ± 1.75	1.21 ± 1.70	1.16 ± 1.36	0.96 ± 1.60	.67	.02

Note. [A] As tested by non-parametric Kruskal Wallis test (ANOVA assumptions were violated). [B] n=1 is missing. [C] n=4 missing. [D] n=2 missing. [E] Not within past 2 months, moreover, an extensive history of levocetirizine use was considered ground for exclusion. [F] Analysis corrected for the amount of time passed between histamine iontophoresis and measurement of the variable. [G] Calculated as post-histamine iontophoresis skin temperature – control. [H] Analysis corrected for pre-conditioning (baseline) variable. [I] Analysis corrected for pre-conditioning (baseline) variable, as well as for the amount of time passed between histamine iontophoresis and measurement of the variable.

Supplementary Table S2. Mixed between-within subjects repeated measures (RMA) results, means, and standard deviations for the combined conditioned groups vs the combined control groups

									Mixed between-within subjects RMA results								
Variables	**Evocation day 1**			**Evocation day 2**		**Evocation day 3**			**Group**			**Group x time**			**Time**		
	Pre-CS	**+30 min**	**+60 min**	**+30 min**	**+60 min**	**+30 min**	**+60 min**	**+90 min**	**F**	***p***	**η²**	**F**	***p***	**η²**	**F**	***p***	**η²**
Physiological outcome parameters																	
Spirometry: FVC % predicted																	
Combined conditioned groups (n=24)	101.8 ± 11.0	101.7 ± 11.4	102.5 ± 12.2	100.9 ± 11.7	100.6 ± 11.7	100.5 ± 12.4	100.4 ± 11.9	100.8 ± 11.8	2.4	.13	.05	0.6	.75	.10	2.1	.06	.28
Combined control groups (n=23)	107.1 ± 12.0	107.5 ± 12.0	107.7 ± 11.7	105.3 ± 12.2	105.4 ± 12.7	105.7 ± 12.6	106.1 ± 11.9	106.7 ± 11.6									
Spirometry: FEV_{1} % predicted																	
Combined conditioned groups (n=24)	94.7 ± 8.8	94.4 ± 9.7	94.8 ± 9.9	95.2 ± 10.5	94.0 ± 9.9	93.5 ± 9.9	93.7 ± 9.5	93.7 ± 9.9	2.3	.14	.05	1.0	.43	.16	1.5	.20	.21
Combined control groups (n=23)	99.4 ± 10.1	99.5 ± 10.0	98.8 ± 10.6	98.4 ± 10.3	97.8 ± 11.0	98.2 ± 11.4	98.5 ± 10.8	98.3 ± 10.7									
Mean heart rate (in BPM)																	
Combined conditioned groups (n=44)	76.3 ± 11.1	71.6 ± 9.6 ***	72.1 ± 8.5 ***	73.6 ± 8.0	73.5 ± 8.0	74.5 ± 8.9	73.4 ± 8.0	66.1 ± 8.3 ***	3.0	.084	.03	2.4	.03	.17	25.4	<.001	.69
Combined control groups (n=44)	74.7 ± 10.9	71.0 ± 9.4 ***	69.7 ± 8.9 ***	70.6 ± 9.1 ***	69.3 ± 8.3 ***	71.0 ± 9.3 †	68.4 ± 9.5 ***	69.8 ± 8.3 ***									
Skin conductance level																	
Combined conditioned groups (n=41)	3.3 ± 2.0	4.2 ± 2.3	4.2 ± 2.2	4.4 ± 2.9	4.4 ± 2.8	4.4 ± 2.6	4.4 ± 2.6	4.2 ± 2.4	0.6	.43	<.01	1.0	.44	.08	8.2	<.001	.43
Combined control groups (n=44)	3.9 ± 2.3	4.9 ± 2.6	4.8 ± 2.1	4.6 ± 2.2	4.4 ± 2.0	4.9 ± 2.1	4.6 ± 1.9	4.2 ± 1.8									
Psychological outcome parameters																	
Positive Affect (PANAS PA)																	
Combined conditioned groups (n=46)	25.5 ± 7.9	25.1 ± 8.2	25.7 ± 8.8	24.0 ± 6.8	25.3 ± 7.6	23.7 ± 7.1	24.6 ± 7.9	24.9 ± 7.9	0.8	.36	<.01	0.6	.78	.05	5.3	<.001	.31
Combined control groups (n=45)	23.9 ± 7.5	22.7 ± 7.8	24.9 ± 7.6	22.2 ± 7.8	23.7 ± 9.3	22.5 ± 7.9	23.8 ± 8.8	24.1 ± 7.8									
State anxiety (STAI-S-s)																	
Combined conditioned groups (n=46)	31.0 ± 9.4	29.6 ± 8.8	31.0 ± 8.3	29.6 ± 7.8	30.4 ± 7.3	29.2 ± 7.4	31.2 ± 8.3	30.1 ± 7.5	1.1	.30	.01	0.7	.69	.05	2.8	.01	.19
Combined control groups (n=45)	31.9 ± 8.1	30.5 ± 6.6	32.5 ± 8.2	31.1 ± 7.6	32.0 ± 8.1	31.8 ± 8.8	31.8 ± 7.5	32.4 ± 7.1									
General wellbeing (NRS)																	
Combined conditioned groups (n=46)	5.7 ± 0.8	5.9 ± 0.8	5.9 ± 0.8	6.0 ± 0.7	5.9 ± 0.6	6.1 ± 0.7	6.0 ± 0.7	5.9 ± 0.7	<0.01	.96	<.01	1.4	.23	.10	10.3	<.001	.46
Combined control groups (n=45)	5.9 ± 0.8	6.0 ± 0.8	5.9 ± 0.9	6.0 ± 0.7	6.0 ± 0.8	6.0 ± 0.8	6.0 ± 0.8	5.8 ± 0.7									

Note. † p<.10, * p<.05, ** p<.01, and *** p<.001 vs variables at the pre-CS level on evocation day 1 (post-hoc within subjects RMA for separate groups).

CS = conditioned stimulus, RMA=repeated measures analysis, $FVC_{\%\ predicted}$ = forced volume capacity (as calculated percentage of predicted values), $FEV_{1\ \%\ predicted}$ = forced expiratory volume in 1 second (as calculated percentage of predicted values), BPM = beats per minute, PANAS PA = Positive Affect and Negative Affect Schedule – Positive Affect, STAI-S-s = State Trait Anxiety Index – State Anxiety, NRS = Numeric Rating Scales

Supplementary Table S3. Mixed between-within subjects repeated measures (RMA) results, means, and standard deviations for the separate group comparison

									Mixed between-within subjects RMA results								
Variables	**Evocation day 1**			**Evocation day 2**		**Evocation day 3**			**Group**			**Group x time**			**Time**		
	Pre-CS	**+30 min**	**+60 min**	**+30 min**	**+60 min**	**+30 min**	**+60 min**	**+90 min**	**F**	***p***	**η²**	**F**	***p***	**η²**	**F**	***p***	**η²**
Physiological outcome parameters																	
Spirometry: FVC % predicted																	
Open-label conditioned group (n=12)	99.9 ± 10.1	99.7 ± 11.4	99.8 ± 11.3	99.9 ± 9.8	99.2 ± 9.8	97.8 ± 10.9	98.8 ± 9.9	99.4 ± 11.4									
Closed-label conditioned group (n=12)	103.8 ± 11.8	103.7 ± 11.6	105.2 ± 13.0	101.9 ± 13.7	102.1 ± 13.6	103.2 ± 13.6	102.1 ± 13.9	102.3 ± 12.5	1.0	.40	.07	1.1	.34	.17	2.1	.072	.28
CNE control group (n=12)	106.6 ± 10.3	106.9 ± 10.5	106.9 ± 10.0	104.4 ± 10.3	104.1 ± 10.8	105.3 ± 9.9	105.7 ± 9.5	106.7 ± 8.8									
Non-conditioned control group (n=11)	107.7 ± 14.1	108.1 ± 14.0	108.5 ± 13.7	106.2 ± 14.4	106.9 ± 14.9	106.2 ± 15.5	106.6 ± 14.6	106.6 ± 14.5									
Spirometry: FEV_{1} % predicted																	
Open-label conditioned group (n=12)	93.8 ± 8.4	92.9 ± 9.6	93.1 ± 9.4	93.8 ± 9.0	92.8 ± 9.1	91.8 ± 8.7	92.3 ± 7.3	92.1 ± 9.2									
Closed-label conditioned group (n=12)	95.7 ± 9.4	95.9 ± 10.0	96.5 ± 10.4	96.6 ± 12.1	95.3 ± 10.9	95.3 ± 11.1	95.0 ± 11.5	95.3 ± 10.6	2.0	.13	.12	0.6	.89	.10	1.4	.23	.21
CNE control group (n=12)	95.9 ± 8.5	96.3 ± 8.3	95.3 ± 9.0	94.9 ± 9.2	93.9 ± 9.3	95.0 ± 10.6	95.0 ± 9.4	95.3 ± 9.7									
Non-conditioned control group (n=11)	103.3 ± 10.7	103.1 ± 10.9	102.6 ± 11.2	102.2 ± 10.6	102.0 ± 11.5	101.6 ± 11.6	102.4 ± 11.2	101.6 ± 11.1									
Mean heart rate (in BPM)																	
Open-label conditioned group (n=21)	78.9 ± 10.1	73.9 ± 9.7 **	73.8 ± 9.1 *	74.7 ± 7.5	74.4 ± 7.4	75.4 ± 8.9	73.5 ± 8.3 *	70.1 ± 7.3 ***									
Closed-label conditioned group (n=23)	73.9 ± 11.8	69.5 ± 9.2 *	70.6 ± 7.7	72.7 ± 8.4	72.6 ± 8.5	73.8 ± 9.1	73.2 ± 7.9	69.5 ± 7.7	1.4	.25	.05	1.7	.026	.13	25.1	<.001	.69
CNE control group (n=23)	74.4 ± 11.2	70.3 ± 9.6 **	68.1 ± 8.8 ***	71.0 ± 8.5	68.8 ± 8.3 **	71.1 ± 9.8	67.1 ± 9.2 **	65.6 ± 7.9 ***									
Non-conditioned control group (n=21)	75.0 ± 10.8	71.7 ± 9.3	71.5 ± 8.9	70.3 ± 9.8	69.7 ± 8.4	70.9 ± 9.0	69.8 ± 9.8	66.6 ± 8.9 ***									
Skin conductance level																	
Open-label conditioned group (n=18)	3.2 ± 1.8	3.9 ± 1.8	3.9 ± 1.7	4.6 ± 3.2	4.6 ± 3.1	4.4 ± 2.8	4.1 ± 2.4	4.1 ± 2.3									
Closed-label conditioned group (n=23)	3.4 ± 2.2	4.4 ± 2.7	4.4 ± 2.6	4.2 ± 2.8	4.2 ± 2.5	4.5 ± 2.5	4.6 ± 2.7	4.3 ± 2.5	0.2	.87	<.01	1.0	.53	.08	7.9	<.001	.43
CNE control group (n=23)	3.8 ± 2.3	5.1 ± 2.8	4.8 ± 1.9	4.7 ± 2.3	4.6 ± 1.9	4.9 ± 1.8	4.6 ± 1.6	4.3 ± 1.6									
Non-conditioned control group (n=21)	4.0 ± 2.4	4.7 ± 2.4	4.8 ± 2.4	4.6 ± 2.3	4.3 ± 2.2	4.8 ± 2.5	4.6 ± 2.2	4.2 ± 2.1									
Psychological outcome parameters																	
Positive Affect (PANAS PA)																	
Open-label conditioned group (n=23)	23.2 ± 8.1	22.3 ± 7.7	23.2 ± 8.4	21.8 ± 6.9	22.6 ± 7.0	22.0 ± 7.4	21.7 ± 6.9	23.1 ± 7.3									
Closed-label conditioned group (n=23)	27.9 ± 7.0	27.9 ± 7.8	28.2 ± 8.7	26.1 ± 6.3	28.0 ± 7.3	25.5 ± 6.5	27.6 ± 7.8	26.7 ± 8.3	2.1	.11	.07	0.7	.88	.05	5.2	<.001	.31
CNE control group (n=23)	23.6 ± 6.3	22.7 ± 6.7	24.7 ± 7.3	21.7 ± 6.9	23.3 ± 9.2	22.1 ± 7.2	22.6 ± 8.6	23.4 ± 7.3									
Non-conditioned control group (n=22)	24.3 ± 8.7	22.7 ± 9.0	25.1 ± 8.1	22.8 ± 8.8	24.2 ± 9.5	23.0 ± 8.7	25.0 ± 9.1	24.9 ± 8.3									
State anxiety (STAI-S-s)																	
Open-label conditioned group (n=23)	32.9 ± 10.6	31.6 ± 9.3	32.3 ± 9.3	30.3 ± 8.5	30.1 ± 8.7	28.8 ± 7.8	30.3 ± 8.4	29.1 ± 8.2									
Closed-label conditioned group (n=23)	29.1 ± 7.9	27.7 ± 8.1	29.7 ± 7.0	29.0 ± 7.1	30.6 ± 5.8	29.6 ± 7.1	32.2 ± 8.3	31.0 ± 6.8	0.8	.49	.03	1.1	.33	.09	2.8	.013	.19
CNE control group (n=23)	30.7 ± 8.4	28.7 ± 6.7	31.0 ± 9.6	29.4 ± 7.1	30.7 ± 8.5	30.7 ± 9.6	31.2 ± 8.0	32.8 ± 7.2									
Non-conditioned control group (n=22)	33.2 ± 7.8	32.4 ± 6.1	34.1 ± 6.3	32.9 ± 7.8	33.3 ± 7.5	32.9 ± 8.1	32.4 ± 7.1	32.1 ± 7.1									
General wellbeing (NRS)																	
Open-label conditioned group (n=23)	5.5 ± 0.9	5.8 ± 0.9	5.8 ± 0.9	6.0 ± 0.7	5.9 ± 0.7	6.1 ± 0.8	6.0 ± 0.8	5.9 ± 0.7									
Closed-label conditioned group (n=23)	5.8 ± 0.7	6.1 ± 0.8	6.0 ± 0.8	6.1 ± 0.6	6.0 ± 0.6	6.1 ± 0.6	6.0 ± 0.7	5.9 ± 0.7	0.2	.89	<.01	1.0	.47	.08	10.5	<.001	.48

CNE control group (n=23)	5.9 ± 0.8	6.0 ± 0.8	5.9 ± 1.0	6.1 ± 0.7	6.0 ± 0.8	6.0 ± 0.9	6.0 ± 0.9	5.8 ± 0.8
Non-conditioned control group (n=22)	5.8 ± 0.7	5.9 ± 0.7	5.8 ± 0.7	5.9 ± 0.7	5.9 ± 0.8	5.9 ± 0.6	5.9 ± 0.8	5.9 ± 0.7

Note. † p<.10, * p<.05, ** p<.01, and *** p<.001 vs variables at the pre-CS level on evocation day 1 (post-hoc within subjects RMA for separate groups).

CS = conditioned stimulus, RMA=repeated measures analysis, CNE = conditioned-not-evoked, $FVC_{\%\ predicted}$ = forced volume capacity (as calculated percentage of predicted values), $FEV_{1\ \%\ predicted}$ = forced expiratory volume in 1 second (as calculated percentage of predicted values), BPM = beats per minute, PANAS PA = Positive Affect and Negative Affect Schedule – Positive Affect, STAI-S-s = State Trait Anxiety Index – State Anxiety, NRS = Numeric Rating Scales

Supplementary Table S4. Suspected medication intake in each session, and comparison of evocation vs. baseline itch by group.

						Group comparison [C]			
		Open-label conditioned group (n=23) [A]	**Closed-label conditioned group (n=23) [A]**	**Conditioned-not-evoked control group (n=23) [A]**	**Non-conditioned control group (n=22) [A]**	**Open-label conditioned group included**		**Open-label conditioned group excluded**	
						χ^2	*p*	χ^2	*p*
Acquisition									
Session 1.	Levocetirizine	73.9 (17)	30.4 (7)	34.8 (8)	59.1 (13)	11.63	.009	4.40	.11
	Placebo	26.1 (6)	69.6 (16)	65.2 (15)	40.9 (9)				
Session 2	Levocetirizine	73.9 (17)	39.1 (9)	34.8 (8)	45.5 (10)	8.57	.036	0.54	.76
	Placebo	26.1 (6)	60.9 (14)	65.2 (15)	54.5 (12)				
Session 3.	Levocetirizine	69.6 (16)	30.4 (7)	47.8 (11)	45.5 (10)	7.18	.066	1.68	.43
	Placebo	30.4 (7)	69.6 (16)	52.2 (12)	54.5 (12)				
Evocation									
Session 1.	Levocetirizine	17.4 (4)	39.1 (9)	34.8 (8)	50.0 (11)	5.47	.14	1.14	.57
	Placebo	82.6 (19)	60.9 (14)	65.2 (15)	50.0 (11)				
Session 2	Levocetirizine	17.4 (4)	47.8 (11)	39.1 (9)	54.5 (12)	7.45	.059	1.08	.58
	Placebo	82.6 (19)	52.2 (12)	60.9 (14)	45.5 (10)				
Session 3.	Levocetirizine	13.0 (3)	47.8 (11)	34.8 (8)	45.5 (10)	7.58	.056	0.91	.64
	Placebo	87.0 (20)	52.2 (12)	65.2 (15)	54.5 (12)				
Comparison of evocation vs. baseline itch									
Mean itch	A lot less itch	4.3 (1)	8.7 (2)	4.5 (1) [B]	9.1 (2)	13.41	.15	6.56	.36
	Somewhat less itch	65.2 (15)	56.5 (13)	36.4 (8) [B]	54.5 (12)				
	Comparable itch	30.4 (7)	8.7 (2)	36.4 (8) [B]	13.6 (3)				
	Somewhat more itch	0.0 (0)	26.1 (6)	22.7 (5) [B]	22.7 (5)				
	A lot more itch	0.0 (0)	0.0 (0)	0.0 (0) [B]	0.0 (0)				

Note. [A] depicted as % (n). [B] Corrected for n=1 missing values. [C] Groups were compared using Chi-Square tests.

Supplementary Table S5. Relation between suspected medication intake during the final evocation session and histamine iontophoresis outcome measures.

	Suspected medication intake during the final evocation session							
	Open-label conditioned group included				**Open-label conditioned group excluded**			
	Levocetirizine (*n*=32)	**Placebo (*n*=59)**	**AN(C)OVA outcomes**		**Levocetirizine (*n*=29)**	**Placebo (*n*=39)**	**AN(C)OVA outcomes**	
			p	**$\eta^2_{partial}$**			***p***	**$\eta^2_{partial}$**
Process measure								
Expected itch [A]	4.42 ± 1.94	3.80 ± 2.02	.76	< .01	4.45 ± 1.90	4.18 ± 1.90	.29	.02
Primary outcome								
Mean itch [A]	2.82 ± 1.93	3.02 ± 1.67	.054	.04	2.93 ± 1.96	3.23 ± 1.68	.016	.09
Secondary outcomes								
Subjective skin response [A]	23.06 ± 11.82	25.42 ± 13.44	.017	.06	24.00 ± 12.01	26.21 ± 13.44	.030	.07
Wheal area (cm^2) [B]	10.87 ± 2.97	10.33 ± 3.44	.59	< .01	10.85 ± 3.11	9.96 ± 3.56	.88	< .01
Flare area (cm^2) [B]	46.34 ± 14.12	44.74 ± 11.52	.59	< .01	45.15 ± 13.92	44.99 ± 11.05	.86	< .01
Change in skin temperature (°C) [A,C]	1.33 ± 1.70	1.13 ± 1.54	.54	< .01	1.28 ± 1.76	0.99 ± 1.36	.43	.01

Note. [A] Analysis corrected for pre-conditioning (baseline) variable. [B] Analysis corrected for pre-conditioning (baseline) variable, as well as for the amount of time passed between histamine iontophoresis and measurement of the variable. [C] Calculated as post-histamine iontophoresis skin temperature – control.

Supplementary Table S6. Means and standard deviations of the individual characteristics of the sample group, with analysis of variance (ANOVA) outcome and calculated Cronbach's alpha for the subscales.

	Combined groups				**Separate groups**						
	ANOVA								ANOVA		
	Conditioned groups (*n*=46)	Control groups (*n*=45)	F	*p*	Open-label conditioned group (*n*=23)	Closed-label conditioned group (*n*=23)	Conditioned-not-evoked control group (*n*=23)	Non-conditioned control group (*n*=22)	F	*p*	Cronbach's α scale
Optimism [A]	18.33 ± 2.72	16.93 ± 2.67	6.07	.016	18.17 ± 2.67	18.48 ± 2.81	16.65 ± 2.96	17.23 ± 2.37	2.21	.093	.68
Perceived stress [B]	8.83 ± 4.28	9.76 ± 4.26	1.08	.30	8.52 ± 4.09	9.13 ± 4.54	9.61 ± 4.08	9.91 ± 4.55	0.45	.72	.78
Worrying [C]	37.93 ± 10.14	38.84 ± 10.90	0.17	.68	38.39 ± 9.57	37.48 ± 10.88	37.87 ± 10.91	39.86 ± 11.05	0.22	.89	.92
Behavioral activation: drive [D]	10.30 ± 2.44	11.02 ± 1.94	2.40	.13	10.13 ± 2.77	10.48 ± 2.11	10.74 ± 1.91	11.32 ± 1.99	1.14	.34	.70
Behavioral activation: fun seeking [D]	10.50 ± 1.72	10.91 ± 1.92	1.16	.29	10.39 ± 1.73	10.61 ± 1.75	10.87 ± 2.18	10.95 ± 1.65	0.44	.73	.46
Behavioral activation: reward responsiveness [D]	17.24 ± 1.77	16.76 ± 1.72	1.75	.19	17.43 ± 1.70	17.04 ± 1.85	17.30 ± 1.77	16.18 ± 1.50	2.42	.072	.53
Behavioral inhibition [D]	18.57 ± 4.03	18.44 ± 4.11	0.02	.89	19.35 ± 4.18	17.78 ± 3.80	18.35 ± 4.01	18.55 ± 4.31	0.58	.63	.83

[A] Assessed by the Life Orientation Test – revised (LOT-R (25), [B] Assessed by the Perceived Stress Scale (PSS (26), [C] Assessed by the Penn State Worry Questionnaire (PSWQ (27), [D] Assessed by the Behavioural Inhibition System / Behavioural Approach System scales (BIS/BAS scales (22)

Supplementary Table S7. Moderation by individual characteristics for the effects of the combined conditioned groups on self-reported itch during iontophoresis in the evocation phase, controlled for baseline, using the PROCESS moderation method.

Variable	Coefficient	t	*p*	Bootstrap LLCI	Bootstrap ULCI	R-square model
Model 1: moderation by optimism [A]						
Conditioning (group)	-0.39	-1.67	.11	-0.88	0.09	
Optimism [B]	0.07	1.14	.26	-0.05	0.20	.62
Conditioning x optimism	-0.09	-1.01	.31	-0.27	0.09	
Model 2: moderation by perceived stress [A]						
Conditioning (group)	-0.34	-1.41	.16	-0.81	0.14	
Perceived stress [C]	0.03	0.79	.43	-0.05	0.11	.61
Conditioning x perceived stress	-0.05	-0.90	.37	-0.16	0.06	
Model 3: moderation by worrying [A]						
Conditioning (group)	-0.33	-1.40	.16	-0.80	0.14	
Worrying [D]	-0.02	-1.16	.25	-0.05	0.01	.61
Conditioning x worrying	0.03	1.15	.25	-0.02	0.07	
Model 4: moderation by BAS drive [A]						
Conditioning (group)	-0.38	-1.59	.12	-0.85	0.10	
BAS drive [E]	0.07	0.85	.40	-0.10	0.25	.61
Conditioning x BAS drive	-0.15	-1.38	.17	-0.37	0.07	
Model 5: moderation by BAS fun seeking [A]						
Conditioning (group)	-0.36	-1.51	.13	-0.84	0.11	
BAS fun seeking [E]	-0.06	-0.70	.49	-0.25	0.12	.61
Conditioning x BAS fun seeking	0.04	0.27	.78	-0.23	0.30	
Model 6: moderation by BAS reward responsiveness [A]						
Conditioning (group)	-0.36	-1.52	.13	-0.82	0.11	
BAS reward responsiveness [E]	0.12	1.21	.23	-0.08	0.31	.63
Conditioning x BAS reward responsiveness	-0.27	-1.96	.053 †	-0.54	0.003	
Model 7: moderation by behavioral inhibition (BIS) [A]						
Conditioning (group)	-0.34	-1.44	.15	-0.81	0.13	
BIS [E]	0.01	0.24	.81	-0.07	0.09	.61
Conditioning x BIS	0.03	0.50	.62	-0.09	0.15	

Note. [A] Model controlled for mean itch during baseline histamine iontophoresis. In all models, itch during baseline iontophoresis was strongly related to itch during evocation (all $p < .001$). This association causes the high explained variance in the model. [B] Assessed by the Life Orientation Test – revised (LOT-R (25), [C] Assessed by the Perceived Stress Scale (PSS (26), [D] Assessed by the Penn State Worry Questionnaire (PSWQ (27), [E] Assessed by the Behavioural Inhibition System / Behavioural Approach System scales (BIS/BAS scales (22). † $p<.10$. LLCI = lower limit confidence interval. ULCI = upper limit confidence interval.

Supplementary Table S8. Moderation by individual characteristics for the effects of the separate groups on self-reported itch during iontophoresis in the evocation phase, controlled for baseline, using the PROCESS moderation method.

Variable	Coefficient	t	*p*	Bootstrap LLCI	Bootstrap ULCI	R-square model
Model 1: moderation by optimism:						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.46	-1.36	.18	-1.13	0.21	
Optimism [B]	> -0.01	-0.01	.99	-0.10	0.10	.62
Conditioning x optimism	0.11	1.06	.29	-0.10	0.31	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	0.05	0.15	.88	-0.62	0.72	
Optimism [B]	0.09	1.75	.084 †	-0.01	0.19	.64
Conditioning x optimism	-0.23	-2.35	.021 *	-0.42	-0.04	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.35	1.00	.32	-0.35	1.04	
Optimism [B]	< 0.01	0.09	.93	-0.10	0.11	.62
Conditioned-not-evoked x optimism	0.07	0.73	.47	-0.12	0.26	
Model 2: moderation by perceived stress						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.47	-1.41	.16	-1.14	0.94	
Perceived stress [C]	0.03	1.01	.32	-0.03	0.09	.63
Conditioning x perceived stress	-0.12	-1.79	.077 †	-0.25	0.01	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	0.02	0.05	.96	-0.66	0.70	
Perceived stress [C]	< 0.01	-0.13	.90	-0.07	0.06	.62
Conditioning x perceived stress	0.04	0.54	.59	-0.09	0.16	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.27	0.80	.43	-0.40	0.94	
Perceived stress [C]	< 0.01	0.10	.92	-0.06	0.07	.62
Conditioned-not-evoked x perceived stress	0.01	0.16	.87	-0.12	0.14	
Model 3: moderation by worrying						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.42	-1.24	.22	-1.09	0.25	
Worrying [D]	-0.01	-0.45	.65	-0.03	0.02	.62
Conditioning x worrying	0.01	0.18	.86	-0.05	0.06	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	0.02	0.07	.94	-0.65	0.70	
Worrying [D]	-0.01	-0.94	.35	-0.04	0.01	.62
Conditioning x worrying	0.03	1.13	.26	-0.02	0.08	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.25	0.75	.45	-0.42	0.92	
Worrying [D]	> -0.01	-0.04	.97	-0.03	0.03	.62
Conditioned-not-evoked x worrying	-0.02	-0.61	.54	-0.07	0.04	
Model 4: moderation by BAS drive						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.46	-1.33	.19	-1.14	0.23	
BAS drive [E]	0.01	0.08	.94	-0.13	0.14	.62
Conditioning x BAS drive	-0.06	-0.57	.57	-0.28	0.16	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	-0.03	-0.09	.93	-0.71	0.65	
BAS drive [E]	0.01	0.22	.83	-0.11	0.14	.62
Conditioning x BAS drive	-0.15	-1.12	.26	-0.40	0.11	

Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.27	0.79	.43	-0.40	0.94	
BAS drive [E]	-0.04	-0.67	.50	-0.16	0.08	.62
Conditioned-not-evoked x BAS drive	0.11	0.80	.43	-0.17	0.39	
Model 5: moderation by BAS fun seeking						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.43	-1.28	.20	-1.11	0.24	
BAS fun seeking [E]	-0.05	-0.72	.47	-0.20	0.10	.62
Conditioning x BAS fun seeking	0.03	0.20	.84	-0.28	0.34	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	-0.01	-0.02	.98	-0.68	0.67	
BAS fun seeking [E]	-0.05	-0.59	.55	-0.20	0.11	.62
Conditioning x BAS fun seeking	> -0.01	-0.01	.99	-0.33	0.33	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.26	0.78	.44	-0.41	0.93	
BAS fun seeking [E]	-0.05	-0.59	.56	-0.21	0.11	.62
Conditioned-not-evoked x BAS fun seeking	< 0.01	0.02	.97	-0.27	0.28	
Model 6: moderation by BAS reward responsiveness						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.37	-1.08	.28	-1.05	0.31	
BAS reward responsiveness [E]	0.04	0.52	.61	-0.12	0.20	.63
Conditioning x BAS reward responsiveness	-0.28	-1.73	.087 †	-0.60	0.04	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	0.03	0.09	.93	-0.66	0.72	
BAS reward responsiveness [E]	-0.02	-0.21	.83	-0.18	0.15	.62
Conditioning x BAS reward responsiveness	-0.03	-0.22	.83	-0.34	0.27	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.34	1.00	.32	-0.33	1.01	
BAS reward responsiveness [E]	-0.13	-1.58	.12	-0.29	0.03	.64
Conditioned-not-evoked x BAS reward responsiveness	0.37	2.37	.020 *	0.06	0.67	
Model 7: moderation by behavioral inhibition (BIS)						
Open-label conditioned group dummy [A]						
Open-label conditioning	-0.41	-1.22	.23	-1.08	0.26	
BIS [E]	0.04	1.28	.21	-0.02	0.11	.62
Conditioning x BIS	-0.05	-0.72	.47	-0.18	0.08	
Closed-label conditioned group dummy [A]						
Closed-label conditioning	0.12	0.36	.72	-0.55	0.79	
BIS [E]	0.01	0.19	.85	-0.06	0.07	.63
Conditioning x BIS	0.12	1.64	.10	-0.02	0.25	
Conditioned-not-evoked control group dummy [A]						
Conditioned-not-evoked	0.29	0.83	.41	-0.39	0.95	
BIS [E]	0.03	0.95	.35	-0.04	0.10	.62
Conditioned-not-evoked x BIS	> -0.01	-0.06	.95	-0.14	0.13	

Note. Dummy variables were computed with the non-conditioned control group as reference category. [A] Models controlled for mean itch during baseline histamine iontophoresis, and other dummy variables. In all models, itch during baseline iontophoresis was strongly related to itch during evocation (all $p < .001$). This association causes the high explained variance in the model. [B] Assessed by the Life Orientation Test – revised (LOT-R (25), [C] Assessed by the Perceived Stress Scale (PSS (26), [D] Assessed by the Penn State Worry Questionnaire (PSWQ (27), [E] Assessed by the Behavioural Inhibition System / Behavioural Approach System scales

(BIS/BAS scales (22). † $p<.10$; * $p<.05$. LLCI = lower limit confidence interval. ULCI = upper limit confidence interval.