

Itch induction by audiovisual stimuli and histamine iontophoresis: a randomized, controlled noninferiority study*

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Summary

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Background Previous research has mainly used skin-manipulating methods to induce itch. In comparison, itch induced by audiovisual stimuli lacks direct skin manipulation.

Objectives The aim of this double blind, noninferiority study was to test the experimental hypothesis that itch induced by audiovisual stimuli is noninferior to itch induced by histamine iontophoresis in case of priming and without priming.

Methods In 80 of 160 healthy volunteers itch was induced by histamine iontophoresis, while in the other 80 itch was induced by audiovisual stimulation. Forty people in each group experienced either an initial resting phase or dermal priming. Itch intensity was measured by visual analogue scales, while scratch duration and frequency were video-recorded and evaluated by two independent raters. In addition, itch quality and location were measured by self-report.

Results Itch induced by audiovisual stimuli was inferior to itch induced by histamine iontophoresis in the absence of dermal priming. However, in the case of priming, maximal itch induced by audiovisual stimuli was not inferior to maximal itch induced by histamine iontophoresis. Additionally, differences in itch quality and location were observed.

Conclusions The finding that maximal audiovisually-induced itch was comparable with maximal histamine itch only after priming emphasizes that attention plays a dominant role in mentally-induced itch. The comparability of maximal histamine and audiovisually-induced itch in the case of priming opens up new research opportunities.

What's already known about this topic?

- Itch is a multidimensional sensation that is altered by, among other things, attention.
- To induce itch in basic research, different methods are used, which are partially invasive or cause skin manipulation.
- Noninvasive audiovisual stimuli can be used to induce itch.

What does this study add?

- This study investigated whether itch induced by audiovisual stimuli is noninferior to itch induced by histamine iontophoresis.
- Itch induced by audiovisual stimuli is noninferior with regard to maximal intensity in the case of priming.
- Noninferiority was not shown in the case of no priming, emphasizing the role of attention in itch induction.
- Histamine and audiovisually-induced itch differ in terms of quality and location, but not in affective reaction.

Itch is an unpleasant sensation triggering scratching or the urge to do so.¹ Psychological factors are linked to its intensity.^{2–4}

Physical and psychological methods are available to induce itch in laboratory settings. The former are well established but need the skin to be manipulated. Skin manipulation itself can be unpleasant, possibly resulting in anxiety, which is supposed to affect itch sensation.⁵ Thus, itch induction including skin manipulation might increase itch perception not only through the applied substance, but also, for example, by triggering anxiety. Furthermore, an attentional focus on physical sensations is linked to an increased experience of itch.⁶

Itch induction by histamine iontophoresis is based on the lococutaneous effect of histamine.⁷ Histamine causes the typical triad of itch, wheal and erythema by activating its receptors on itch-conducting mechanosensitive C fibres and the endothelium.^{8–11} Using histamine iontophoresis, maximum itch intensity is usually reached after 3–4 min.^{12,13} The induced itch is tickling, pricking, warm, radiating and localizable, annoying, wavelike and lasts > 15 min. The effects depend on the iontophoresis current.¹²

In addition, itch can be induced by (audio)visual stimuli,^{14–18} without the need to manipulate the skin directly. Various factors are assumed to play a role in this kind of itch induction. Besides classical conditioning, mirror neurons and empathy are discussed as contributing to mentally-induced itch.^{19–22} For sensations induced by substances, it has already been shown that they are altered by attention.^{6,23} It is reasonable that itch induction by the presentation of audiovisual itch depends even more on the subjects' attention, as only focusing on the stimuli and the skin should have an effect. Thus, priming on the skin could be a strategy to alter audiovisually-induced itch. Indeed, in our previous studies we noticed that induced itch was more intense when a skin-related control video was shown before and not after audiovisual itch stimuli. However, we did not investigate this effect systematically.

So far, there have been studies comparing the effectiveness of different substance-dependent itch-inducing methods.^{24–26} However, no study thus far has compared mental induction to substance-dependent methods. Therefore, we aimed to test whether audiovisually-induced itch is noninferior to itch induced by histamine iontophoresis. Our experimental hypothesis (H1) was not a superiority hypothesis, but a noninferiority one. Subsequently, the effect of shifting attention toward the skin (dermal priming) before itch induction was investigated.

As there have been no studies describing the quality of audiovisually-induced itch and only a few describing the quality of itch induced by histamine,^{25,26} a secondary aim was to assess the quality and location of induced itch.

Patients and methods

Participants

In total, 160 healthy volunteers were recruited. Each volunteer received €20 for participation in the study. Volunteers had to

be aged 18–30 years in order to be included. During an initial telephone interview, volunteers were screened for the following exclusion criteria: participation in preliminary studies at our institute; prior participation in stress-management trainings; current psychiatric/neurological diseases; chronic physical illness; use of a cardiac pacemaker; adrenal or thyroid diseases; allergies; previous anaphylactic reactions; hay fever/bronchial asthma; immune system disorders; skin diseases, infections or other current diseases; vaccinations within the last 3 months; current mosquito bites; the current use of medically indicated medications/ointments (Fig. S1; see Supporting Information).

Study design

This double-blind, randomized study consisted of two sub-studies. In study 1(a), 80 participants rested for 10 min (no dermal priming) before itch was induced either by histamine iontophoresis [histamine gel + neutral video 2 (NV2): control group (CG); *n* = 40; resting-histamine] or audiovisual itch stimuli [placebo gel + experimental video (EV): experimental group (EG); *n* = 40; resting-audiovisual itch]. In study 1(b) (dermal priming), all 80 participants watched a non-itch-inducing skin-related video [neutral video 1 (NV1)] before itch induction [either presentation of a non-itch-inducing NV2 + histamine iontophoresis: CG (*n* = 40; priming-histamine) or presentation of the EV + placebo gel: EG (*n* = 40; priming-audiovisual itch)]. Randomization was conducted by a person not involved in data collection by drawing a closed envelope out of a bigger envelope including a card with a number. The number informed the investigators (R.M., G.R.) which video had to be presented and what gel tube had to be applied. Groups were stratified according to age and sex. The investigators were blinded to the content of the gel and the video. To blind study participants to the study aim, they were told that 'male and female healthy participants will be randomly assigned to one of two experimental conditions (presentation of different videos and application of different substances on the skin) and will be asked to report their current bodily sensations and emotions. We are interested in whether groups differ regarding the relationship between bodily sensations and emotions'. Regarding iontophoresis, they were told that 'the experimenter will apply two electrodes to the forearm, which include a substance that can evoke, increase or reduce one or more of the sensory qualities and emotions we are interested in'. Regarding the camera, the information that 'during the investigation you will be filmed by use of a video camera in order to be able to rate your mimics and gestures during the investigation' was included in the information sheet. Participants were informed about the real intention of the study at the end of the investigation.

Recruitment and data collection took place between August 2013 and April 2014. At the beginning of the investigation, which took place at the Dermatology Clinic of the University of Giessen, each participant was seated on a leather armchair, 3.5 m from a 2 × 2 m screen and asked to remove his/her

bracelets. Then the exclusion criteria were reviewed again. Afterwards, the participant was video-recorded for 10 min while resting [study 1(a)] or being presented NV1 [study 1(b)]. Afterwards, participants had to rate the sensations and emotions they had in the previous 10 min and at the current moment. During the subsequent itch induction period, the participant was video-recorded and afterwards, sensations and emotions were assessed again. In addition, questionnaires measuring itch characteristics and psychological variables were completed (Table 1).

Itch induction

In the CG, itch was induced by histamine iontophoresis, which was followed by a non-itch-inducing video on the skin (NV2). In the EG, itch was induced by an EV on itch, which was started after application of the placebo gel. NV2 contained nine static pictures: a baby's hand touching the hand of an adult; a naked woman and man sitting in the nature in front of a waterfall; the face of a woman taking a shower; a female and male hand almost touching each other; the faces of two Barbie dolls with perfect skin; a baby's feet and a mother's feet walking on a white blanket; two cats cuddling each other; a woman lying in a bath tub; and six feet (two from a father, four from children) under a comforter. During the presentation of the pictures, the speaker (U.G.) talked in the background about the skin as the organ of communication, the role of touching for babies, tactile sensors of the skin, the fact that humans mainly consist of water, and so on. The EV included nine static pictures: a female scratching her back; ants crawling on a white surface; a bloody mosquito bite on a hand and a mosquito; skin that was scratched after a mosquito bite; a big bug; two monkeys lousing each other; a human flea; and flea bites on a human's back (two pictures). While

the pictures were displayed, the speaker (U.G.) talked about ants, mosquitos, fleas, bugs, lousing monkeys, that scratching can be a displacement activity in stressful situations, and so on. NV1 [only used in study 1(b)] contained nine static pictures: hands splashing water; a girl wearing sunglasses, a sun hat and having sun lotion on her face; five young adults with different skin types; a man looking in the mirror while putting lotion on his face; a child's hand holding a wrinkled hand; the back of a man with many naevi, being looked at through a magnifying glass by a female dermatologist; the face of a middle-aged woman with a large naevus above her upper lip; a man with a wart beneath his right eye and a young, red-haired woman with many freckles (one picture); and sunlight shining on a cornfield. In the background, a speaker (U.G.) talked about the skin in general, different skin types, sunburn, sun protection, skin screening and the need of sun.

In line with Papoiu et al.,²⁴ iontophoresis was performed with 2% methylcellulose gel in the EG (CG: + 1% histamine) at 200 μ A for 30 s on the nonleading forearm. The electrodes [PF384 Dispersive Electrode and LI611 Drug Delivery Electrode (Perimed, Järfälla, Sweden)] were positioned 5 cm proximal to the wrist at a distance of 15 cm. The application site was cleaned before and after applying the electrodes with kodan[®] tincture forte colourless (Schülke, Norderstedt, Germany) and pulp. Electrodes were removed after 30 s. Immediately after removing the electrodes, either NV2 (in case of histamine application) or EV (in case of placebo gel application) was started.

Assessment of alteration in itch parameters

Maximal itch intensity during itch induction was measured by using the item, 'Please indicate to what extent the following

Table 1 Study procedure

Minute	0-10	10-20	20-23	23-38	38-50	50-60
Study 1a Study 1b	Introduction + consent	Resting (1a) Dermal priming (1b)	Question- naires	Experimental itch induction: either histamine iontophoresis + presentation of non-itch inducing audiovisual stimuli OR presentation of audiovisual itch stimuli + placebo iontophoresis	Question- naires	Debriefing + allowance
Measurement		Scratch movements + duration	Sense qualities and emotions including itch intensity	Scratch movements + duration	Sense qualities and emotions including itch intensity, itch qualities and affective responses to pruritus, psychosocial data, others	

statements applied to you since the application of the gel. Indicate the maximal intensity you perceived: I perceived itch'. Current itch intensity immediately after the itch induction period was measured by the item, 'Please indicate to what extent the following statement currently applies to you: I perceive itch'. These questions were answered on a visual analogue scale [VAS; 0 (not at all) to 10 (very intense)]. The target variable alteration in itch intensity was calculated by subtracting the values obtained from the itch induction period from the corresponding values of the resting phase/priming phase.

To measure scratch movements and scratch duration, participants were filmed during the resting/priming and itch induction periods. All video material was evaluated by two independent raters using observation software (Interact; Mangold International, Arnstorf, Germany). The raters were trained by a dermatologist (U.G.) on differentiating scratching from touching. Afterwards, determination of the number of scratch movements and scratch duration reliability analyses were conducted for both measures. These yielded significant inter-rater reliabilities (Cronbach's $\alpha \geq 0.963$).

Assessment of itch characteristics

To assess the location of itch, participants marked the body sites where their itch began and where it spread to. Itch qualities and affective responses to itch were measured on a 5-point Likert scale [0 (not at all) to 4 (always)] by use of a German adaptation of an itch questionnaire based on the McGill pain questionnaire.^{27,28}

Ethics

In conformity with the Declaration of Helsinki, the study design was approved by the local ethics committee of the medical faculty at the University of Giessen (Institutional Review Board approval #46/13). Participants were informed about possible health risks, the study procedure, expense allowance, data security and insurance. Participants were free to withdraw from the study at any time.

Statistical analysis

We aimed to show that itch-related audiovisual itch stimuli are not worse at inducing itch than histamine iontophoresis. Thus, our hypothesis (H1) was that the presentation of audiovisual itch stimuli leads to a comparable increase in itch as histamine iontophoresis. This approach is the opposite of that usually used (superiority hypotheses stating that one group/treatment is better than another).²⁹ We aimed to test our H1 in the case of no and in case of prior priming. As it is impossible to show exact equivalence, a prespecified margin of noninferiority was defined beforehand.^{29,30} We estimated the precision of measurements by using data from our previous research and considerations regarding the standard error measurement. From previously collected data,^{17,31} it was known that the mean \pm SD increase in itch in healthy skin controls after having seen a

non-itch-inducing control video was 2.7 ± 3.1 . Another group found a retest reliability of a VAS measuring itch in patients with chronic itch 0.88.³² A recent study confirmed the reliability of this size for acute histamine-induced itch in healthy controls (intraclass correlation coefficient 0.83–0.93).³³ Thus, the standard error of measurement was calculated as $S_e = 3.1 \sqrt{1-0.88} = 1.07$. The corresponding confidence interval (CI) is $CI = x - 1.96 \times 1.07 = x - 2.10$. Using a conservative approach, we rounded off and set the noninferiority margin a priori to -2 (VAS 0–10). A difference within this limit was interpreted as noninferiority. Taking these values into consideration, we used the following formula to calculate our sample size: $2 \times 3.1^2 (1.96 + 0.84)^2 / (2-0)^2$.^{34,35} It revealed that 38 participants had to be included in each group to achieve a power of 80% with a given α of 0.05. We recruited 40 people per group, in order to account for possible dropouts. Then noninferiority tests were performed according to Walker and Nowacki³⁰: 'non-inferiority is established, at the α significance level, if the lower limit of a $(1-2\alpha) \times 100\%$ CI for the difference (new – current) is above $-\delta$ ', whereby $-\delta$ represents the noninferiority margin. For the manipulation check (could itch be induced by both methods?) and group comparisons t-tests and Pearson χ^2 -tests were conducted using SPSS Statistics 24 (IBM, Armonk, NY, U.S.A.).

Results

Group comparison

In study 1(a) (no priming = resting), each group consisted of 11 men and 29 women.

The mean \pm SD age of those in the CG (resting-histamine) was 23.78 ± 2.77 years, and that of the EG (resting-audiovisual itch stimuli) was 24.73 ± 2.53 years [$t(78) = 1.60$; $P > 0.05$]. Those in the EG had a significantly more intense itch compared with those in the CG during the resting period [EG 0.96 ± 1.42 ; CG 0.41 ± 0.80 (VAS 0–10); $t(61.7) = 2.14$; $P = 0.04$]. No further group differences regarding any other itch parameters were seen.

In study 1(b) (priming), each group consisted of 18 men and 22 women. The mean \pm SD age of those in the CG (priming-histamine) was 23.68 ± 2.96 years, and that of the EG (priming-audiovisual itch stimuli) was 23.80 ± 2.63 years [$t(78) = 0.20$; $P = 0.84$]. Apart from an initially increased level of disgust (VAS 0–10) in the CG during priming [1.14 ± 1.79 vs. 0.43 ± 0.94 ; $t(78) = -2.23$; $P = 0.03$], no further group differences occurred, neither during nor immediately after priming.

A manipulation check revealed that all itch parameters, except for scratch duration, significantly increased from the resting/priming period to itch induction period (Table 2).

Noninferiority testing

Average changes in itch intensity due to the different itch induction methods can be found in Figure 1.

Table 2 Manipulation check itch induction

Condition	Increase in maximal itch intensity (VAS 0–10)	Increase in current itch intensity (VAS 0–10)	Increase in the number of scratch movements	Increase in scratch duration (s)
Resting-audiovisual itch stimuli (n = 40)	2.04 ± 2.46 [T(39) = 5.23; P ≤ 0.001]	1.04 ± 1.54 [T(39) = 4.27; P ≤ 0.001]	1.14 ± 3.06 [T(39) = 2.35; P = 0.02]	2.06 ± 8.94 [T(39) = 1.46; P = 0.15]
Resting-histamine (n = 40)	4.46 ± 3.18 [T(39) = 8.87; P ≤ 0.001]	2.56 ± 3.10 [T(39) = 5.24; P ≤ 0.001]	1.06 ± 2.53 [T(39) = 2.65; P = 0.01]	4.00 ± 13.42 [T(39) = 1.88; P = 0.07]
Priming-audiovisual itch stimuli (n = 40)	2.96 ± 2.81 [T(39) = 6.67; P ≤ 0.001]	1.54 ± 2.14 [T(39) = 4.54; P ≤ 0.001]	2.28 ± 5.97 [T(39) = 2.41; P = 0.02]	5.71 ± 24.78 [T(39) = 1.46; P = 0.15]
Priming-histamine (n = 40)	3.15 ± 2.95 [T(39) = 6.74; P ≤ 0.001]	2.61 ± 3.31 [T(39) = 4.98; P ≤ 0.001]	2.86 ± 5.26 [T(39) = 3.44; P = 0.001]	12.67 ± 84.05 [T(39) = 0.95; P = 0.35]

Average increases in itch parameters due to itch induction (Δ values of itch induction period/values of resting or priming period, respectively). VAS, visual analogue scale.

Study 1(a): The noninferiority test showed that itch induced by audiovisual stimuli was inferior to itch induced by histamine iontophoresis in the case of no priming (mean difference of maximum induced itch -1.52 , with a lower 90% CI bound of -2.43). The mean difference in current itch immediately after itch induction was -2.42 (lower bound 90% CI of -3.48). As these lower bounds of the 90% CI were outside the noninferiority margin, the noninferiority test revealed inferiority of itch induced by audiovisual stimuli vs. itch induced by histamine for study 1(a).

Study 1(b): The noninferiority test showed that maximal itch induced by audiovisual stimuli was not inferior to histamine-induced itch in case of priming, with a mean difference of induced itch of -0.183 (lower bound 90% CI of -1.26), lying within the noninferiority margin of -2 . Noninferiority could not be shown for current itch immediately after the itch induction period, with a mean difference of -1.07 and a lower bound 90% CI of -2.1 (which is outside the noninferiority margin) (Fig. 2).

Location and quality of itch

Owing to the fact that noninferiority of maximal itch induced by audiovisual stimuli was only shown after priming, we focused on the comparison of histamine and audiovisually-induced itch after priming [study 1(b)] only. In contrast to a strictly localized histamine-induced itch at the site of application, itch induced by audiovisual stimuli was observed in multiple regions (Fig. 3). More participants of the CG than of the EG reported that itch began on the arms [EG: n = 14; CG: n = 34 ($\chi^2 = 20.83$, $P < 0.001$)], whereas itch induced by audiovisual stimuli more often than histamine induced itch began on the face [EG: n = 15; CG: n = 5 ($\chi^2 = 6.67$, $P = 0.01$)] or back [EG: n = 4; CG: n = 0 ($\chi^2 = 4.21$, $P = 0.04$)]. For the neck, chest, scalp and anogenital region, no significant differences between the groups were recorded.

In the course of the 10-min itch induction period, more participants of the EG than of the CG experienced itch on their face [EG: n = 30; CG: n = 15 ($\chi^2 = 11.43$; $P < 0.001$)], followed by itch on their hands [EG: n = 12; CG: n = 2 ($\chi^2 = 8.66$, $P < 0.01$)], legs [EG: n = 12; CG: n = 4 ($\chi^2 = 5.00$,

$P = 0.03$], back [EG: n = 11; CG: n = 3 ($\chi^2 = 5.54$, $P = 0.02$)] and feet [EG: n = 9; CG: n = 2 ($\chi^2 = 5.17$, $P = 0.02$)]. Histamine iontophoresis more often led to itch on the arms than audiovisually induced itch [EG: n = 26; CG: n = 40 ($\chi^2 = 16.97$, $P < 0.001$)]. Itch induced by both methods also frequently led to itch on the scalp [EG: n = 16; CG: n = 11 ($\chi^2 = 1.40$, $P = 0.24$)].

Histamine-induced itch was described as more 'biting' [t(65.71) = 2.48; $P = 0.02$], 'painful' [t(67.82) = -3.33 ; $P = 0.001$], 'burning' [t(78) = -2.52 ; $P = 0.01$], 'superficially localized' [t(66.71) = -2.33 , $P = 0.02$] and 'piercing' [t(70.85) = -2.73 ; $P = 0.01$] than audiovisually-induced itch. No other group differences occurred (Fig. 4).

Discussion

As studies have shown, itch can be induced by the presentation of (audio)visual itch stimuli.^{14–18,31} Our study compared itch induced by audiovisual stimuli to itch induced by histamine iontophoresis. We aimed to show that itch induced by audiovisual stimuli is not inferior to itch induced by histamine iontophoresis. We found that audiovisually-induced itch was inferior to histamine-induced itch in case of resting before itch induction (no priming). However, maximal audiovisually-induced itch after priming was comparable with itch induced by histamine iontophoresis. We speculate that attention shifting might thus be especially capable of affecting mental processes. This hypothesis is supported by the fact that an attentional bias towards itch pictures, but not for somatosensory itch stimuli, was recently shown.²³ Our study suggests that the attentional bias towards itch pictures might be strengthened by priming, resulting in noninferiority of audiovisually-induced itch vs. histamine-induced itch.

The fact that noninferiority could only be shown for the time of itch induction itself ('maximal itch during itch induction') and not for the time thereafter ('current itch after itch induction') can possibly be explained by a prolonged effect of locally applied histamine,¹² which has not yet been shown for audiovisually-induced itch. Moreover, as attention is relevant for the intensity of audiovisually-induced itch, it is possible that completing the questionnaires after the itch induction

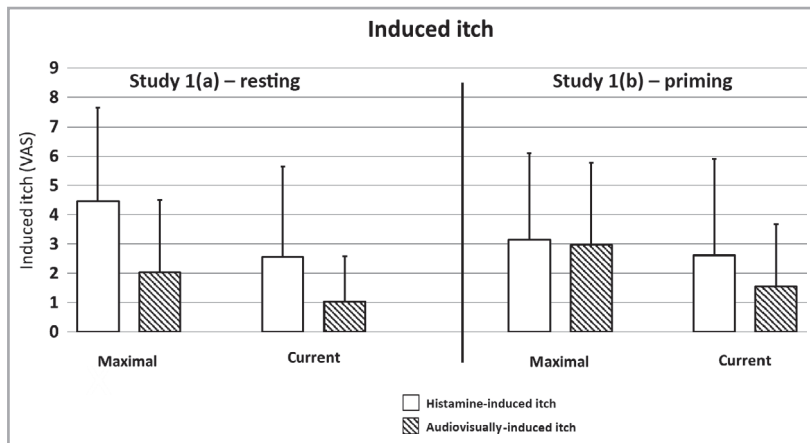


Fig 1. Itch induced by either histamine iontophoresis (white) or audiovisual stimuli (shaded), with or without priming. Maximal itch intensity during the itch induction period minus maximal itch intensity during resting (study 1a) or priming (study 1b) period; current itch intensity immediately after itch induction minus current itch intensity immediately after resting or priming period. Error bars represent the SD of the mean induced itch. VAS, visual analogue scale.

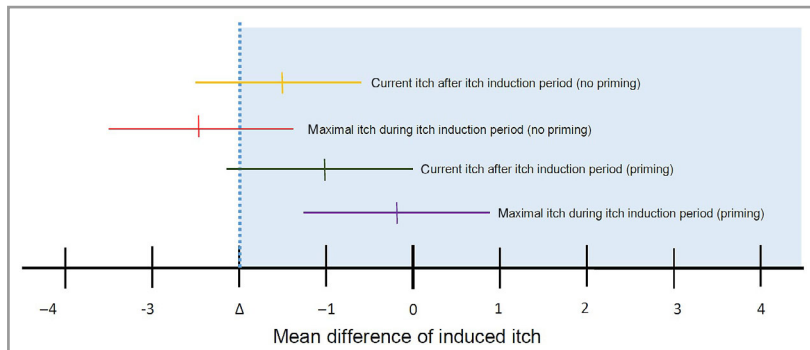


Fig 2. Observed mean differences in induced itch (audiovisually-induced itch minus histamine-induced itch). Error bars indicate two-sided 90% confidence intervals. The blue dashed line indicates the noninferiority margin (-2). The light-blue shaded area to the right of Δ indicates a noninferiority of audiovisual itch; yellow line indicates mean difference of current itch [visual analogue scale (VAS) 0–10] immediately after the itch induction period [study 1(a), no priming]; red line indicates the mean difference of maximum itch (VAS 0–10) during the itch induction period [study 1(a), no priming]; green line indicates the mean difference of current itch (VAS 0–10) immediately after the itch induction period [study 1(b), priming]; purple line indicates the mean difference of maximum itch (VAS 0–10) during the itch induction period [study 1(b), priming].

period has a more reducing effect on audiovisually-induced itch than on itch induced by histamine iontophoresis.

Itch induced by histamine iontophoresis was experienced as more biting, painful, burning, superficially localized and piercing than audiovisually-induced itch. With regard to the location of itch, histamine itch was experienced at the site of application, while itch induced by audiovisual stimuli spread from central to peripheral areas (Fig. 3). This distribution pattern is in line with the findings of other studies.^{15,36} In these studies, the presentation of videos showing other people scratching mainly led to scratching of the face, head and body sites distal from the stimulated forearm.^{15,36} One explanation is that audiovisual itch stimuli activate an emotion-based mirror neuron system, the activation of which results in anxiety/tension, which is then processed/reduced by displacement behaviours such as self-touching or scratching the face and

other distal body sites.^{20,36,37} Another explanation mentioned previously is that ongoing or spontaneous itch-related afferent activity might be overinterpreted as itch when one's attention is centred on itch-related issues.¹⁵ Furthermore, we assume that the number of free nerve endings, illustrated by the sensory homunculus,³⁸ plays a role when it comes to the location of audiovisually-induced itch as high neural resolution increases the risk of spontaneous tension discharges. Our data support this assumption as audiovisually-induced itch mainly occurred in higher-resolution regions.

Interestingly, itch intensities were not significantly correlated with the number of scratch movements after priming [EG: $r = 0.14$ ($P = 0.20$); CG: $r = 0.18$ ($P = 14$)]. This confirms that itch and scratching should not be regarded as co-existent, even though they – per definition – occur together.¹ Previously, small-to-moderate correlations have been

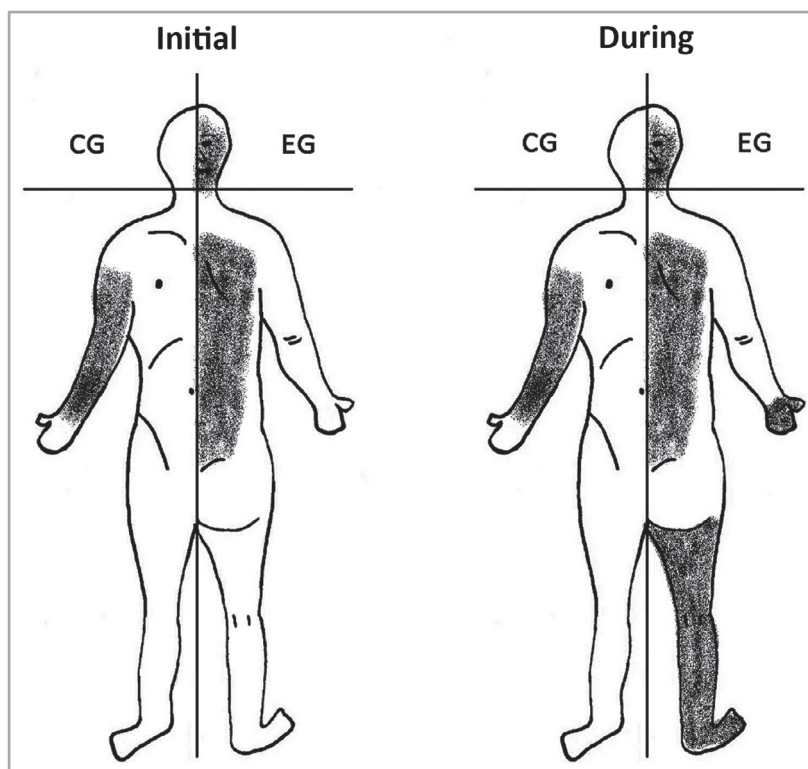


Fig 3. Typical location of induced itch. Grey areas mark the regions for which significant group differences were found regarding the number of persons who felt itch initially and in the course of the itch induction period. (Left) Body sites where itch induced by histamine and audiovisual stimuli typically began (initial); (right) body sites where itch typically occurred during the itch induction period. Left body side: control group (CG; itch induced by histamine iontophoresis); right body side: experimental group (EG; itch induced by audiovisual itch induction).

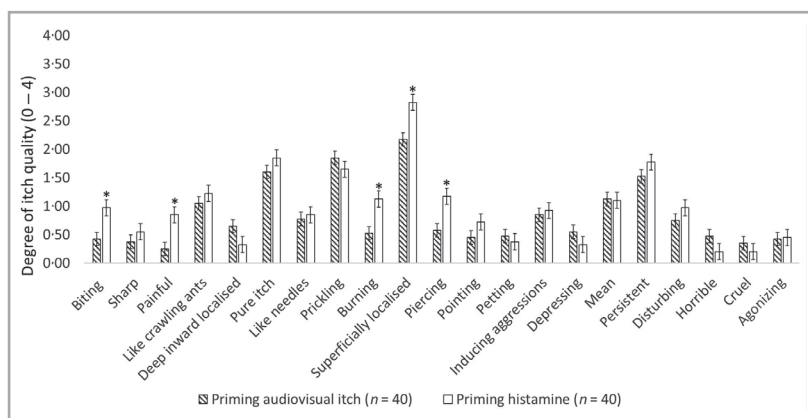


Fig 4. Differences in itch quality, induced by either audiovisual itch stimuli or histamine after priming. *Statistically significant difference ($P < 0.05$).

observed.^{16,39} A possible explanation for the rather low correlations in our study could be that some participants tried to refrain from scratching to avoid a worsening of itch, as they reported afterwards. An additional explanation is that scratching might have also occurred as displacement behaviour with the purpose of lowering tension, which might have differed between participants. The assessment of tension during itch induction should be done in future studies.

This study had some limitations. The participants were rather young and educated. In the future, the sample should be more heterogeneous. Furthermore, as we used a very unspecific manipulation (watching a video vs. resting), we cannot rule out that a mechanism other than priming led to the differences in induced itch in studies 1(a) and 1(b). It would therefore be of advantage to test the effects of dermal priming against the effects of another, more specific

manipulation (e.g. watching a video that shifts attention to another non-skin-related topic). This would also be beneficial, as in this study the baseline values for itch were generally higher in the dermal priming group. However, it is not easy to find a video not evoking positive or negative emotions, which have been shown to be associated with an altered perception of sensations.^{40,41}

In conclusion, this study is the first to show that maximal itch induced by audiovisual itch stimuli is not inferior to itch induced by histamine iontophoresis, but only in case of skin-related priming. Thus, this study gives further insight into the effectivity of itch-inducing methods.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. CONSORT flow diagram.

Powerpoint S1. Journal Club Slide Set.