Acta Derm Venereol 2016; 96: 619–623

INVESTIGATIVE REPORT

Itch Perception and Skin Reactions as Modulated by Verbal Suggestions: Role of Participant's and Investigator's Sex

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This study investigated sex-specific differences in itch perception and skin reactions, as modulated by verbal suggestions, and the role of the investigator's sex. Healthy volunteers (50 males, 50 females), divided into 4 groups, were tested by male and female investigators. Itch was induced via prick testing with sodium chloride and histamine in 4 runs; 2 control conditions (with no exaggerated verbal comments about expected itch) and 2 experimental conditions (with exaggerated verbal comments). After 5 min, wheal and flare reactions were measured and itch intensity was rated by subjects on a numerical rating scale. Exaggerated verbal suggestions resulted in higher itch intensity ratings in the sodium chloride and histamine condition, and higher unpleasantness ratings and a wheal of greater extent in the sodium chloride condition, as well as a flare of greater extent in the histamine condition. The magnitude of the differences between the exaggerated verbal suggestion conditions and respective control conditions was only significantly different between male and female investigators concerning flare size in the histamine condition. There were no differences between male and female participants. Therefore, sex differences may play only a minor role in nocebo-induced itch perception. ***Key words: sex; subject; investigator; pruritus-perception; skin reaction; suggestibility.***

Accepted Dec 20, 2015; Epub ahead of print xx

Acta Derm Venereol 2016; 96: 619–623.

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Although chronic pruritus (longer than 6 weeks' duration (1)) is a bothersome symptom of many diseases, our knowledge of psychological and other factors that influence it are limited (2, 3). There is also little knowledge about sex-specific differences in the perception and evaluation of acute and chronic itch. Ständer et al. showed that female patients experienced chronic itch more intensely than male patients, and that itch was influenced more profoundly by psychological factors in females than in males (4). However, it is not known whether the sex of the physician or investigator in trials can influence itch intensity ratings.

There are conflicting reports of the influence of the sex of the patient or the investigator on patients' intensity ratings of pain. According to Aslaksen et al. (5), males reported lower pain intensities to female than to male investigators. Kallai et al. (6) found that pain was tolerated for longer when subjects were tested by an investigator of the opposite sex, and that higher pain intensities were reported by male patients to female investigators. Vigil et al. (7) found that patients of both sexes demonstrated lower pain sensitivity and higher pain intensity when the investigators were male rather than female. Swider & Babel (8) evaluated the effect of the sex of the model on nocebo hyperalgesia induced by social observational learning. Besides the fact that empathy traits predicted the magnitude of nocebo hyperalgesia, the sex of the model (greater effect in the male model) was important, but not the sex of the participant.

In contrast, in a systematic review of 15 studies by Horing et al. (9), examining predictors for placebo effect, only one study found that sex was a significant predictor of pain response (10).

Itch is thought to be highly susceptible to suggestion (11, 12) and may be influenced by verbal suggestion. Van Laarhoven et al. (13) demonstrated that verbal suggestions, by raising negative expectations, could increase the nocebo effects of histamine, namely itch and pain, while itch could be reduced more than pain by placebo suggestions. Placebo and nocebo effects were most pronounced in a combination of verbal suggestion and conditioning (14). The research group of Klosterhalfen and Enck performed several studies showing that conditioning and habituation are more effective in females, while males are more responsive to suggestion in nausea experiments (15–18). Also, males are more prone than females to placebo analgesia (19–21).

However, suggestions can influence not only perception of itch intensity, but also skin reactions to experimental stimuli, such as histamine injections. Kiecolt-Glaser et al. (22) found that histamine-induced wheal increased when subjects were under stress. Anxiety enhanced the effects of stress even further. In contrast, Kimata (23) did not observe an increased histamine-induced flare after stress in patients with atopic dermatitis. To date, no studies have examined sex-specific differences in pruritus in response to verbal suggestions.

Based on the current literature, this study investigated possible sex-specific differences in itch perception following suggestions that raise expectations of intensity

 doi: 10.2340/00015555-2336
 ISSN 0001-5555

of pruritus (nocebo-like suggestions) and in skin reactions to an experimental itch stimulus.

In line with previous findings (15–18), it was hypothesized that males would be more susceptible to suggestions, resulting in enhanced skin reactions and higher itch ratings. A second hypothesis was that the investigator's sex would play a role in modulating these reactions in healthy subjects.

Four experimental runs were performed under 4 different conditions: 2 control conditions with prick tests with sodium chloride (NaCl) and histamine solutions in combination with neutral verbal instructions; and 2 conditions using the same solutions but with exaggerated verbal instructions (nocebo-like conditions I and II). The participants were divided into 4 groups: a female investigator giving verbal comments to female subjects, a male investigator giving verbal comments to female subjects, a male investigator giving verbal comments to male subjects, and a female investigator giving verbal comments to male subjects.

METHODS

Participants

A total of 100 healthy volunteers (50 females and 50 males) with no history of chronic disease, mean age 24.2 ± 3.7 years, were included in the study. None of the participants had atopic diathesis, and their anxiety sensitivity index (ASI (24)) was < 24. Atopic diathesis was excluded by the Erlangen Score of Diepgen et al. (25). The Anxiety Sensitivity Index is the most widely used instrument to assess anxiety-related sensations. It consists of 16 statements reflecting either distress about anxiety symptoms (e.g. "It scares me when I feel shaky") or concerns about negative consequences of anxiety symptoms (e.g. "When I am nervous, I worry that I might be mentally ill"). The total score can range between 0 and 64. The threshold for an elevated ASI is 24.

All participants gave written informed consent. The study was approved by the local ethics committee.

Study design

Fifty healthy volunteers (25 males and 25 females) were examined by a female and 50 (25 males and 25 females) by a male examiner. Thus, there were 4 groups with 25 participants each.

Each participant underwent 4 prick tests; 2 in the left forearm and 2 in the right forearm. The applied solution was either 20 µl 0.9% sodium chloride (NaCl) solution (2 prick tests) or 20 µl 0.1 mM histamine solution (2 prick tests). The histamine and NaCl prick test was performed once on each forearm. After 5 min participants were asked to record the maximal itch intensity, desire to scratch and unpleasantness of itch, each on a numerical rating scale (NRS) from 0 (no itch/no desire to scratch/no unpleasantness) to 10 (worst itch imaginable/maximum desire to scratch/worst unpleasantness imaginable). Flare and wheal were measured with a measuring tape. The prick test site was covered with a stretched scarf to avoid visual bias of the evaluation of itch intensity. After each run, there was a 30-min interval to avoid interactions between the single conditions. The total duration of the whole experiment was 110 min. Immediately before each prick test, the investigator gave verbal suggestions about what to expect. The order of the runs with the corresponding verbal suggestions and the hypotheses/expectations are described in Table I.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics (Version 22; SPSS Inc., Chicago, Illinois, USA). To compare paired control and nocebo conditions I and II, non-parametric Wilcoxon signed-rank tests were performed for the skin reactions (flare and wheal) and the NRS scores (pruritus intensity, urge to scratch and pruritus unpleasantness). Further analyses included comparisons of the differences between the control and the corresponding experimental condition, once with regard to investigator's sex and once with regard to participant's sex, using Mann–Whitney *U* tests. All statistical analyses were controlled for multiple testing using Benjamini & Hochberg procedures (26).

RESULTS

To confirm the validity of the study design, the whole group of participants was first analysed without stratification according to sex. As expected, a larger wheal developed under nocebo-like condition I (4: NaCl + exaggerated verbal instruction) than under nocebo-like control condition I (1: NaCl + neutral verbal instruction) ($Z=-3.363$, $p=0.001$). Furthermore, participants reported significantly higher itch intensities ($Z=-2.943$, $p = 0.003$) and higher unpleasantness ($Z=-2.993$, $p = 0.003$) under nocebo-like condition I in relation to the corresponding control condition. There were no significant differences in flare size or in ratings of urge to scratch. The nocebo-like experimental condition (3: histamine + exaggerated verbal instruction) and nocebo-like control condition II (2: histamine + neutral verbal instruction) differed in itch intensity ratings ($Z=-2.678$, $p = 0.007$) and in flare size ($Z=-2.333$, $p = 0.02$). Nocebo-like condition II did not differ from nocebo-like control condition II in wheal size or in urge to scratch and feeling of unpleasantness. The results are shown in detail in Table II.

Table I. *Instructions, hypotheses and corresponding conditions*

Run	Application	Verbal instruction	Hypothesis/expectation	Condition
1	NaCl	"I'm going to inject you with a small quantity of a substance that does not cause itch in most people."	No itch sensation	Nocebo-like control I
2	Histamine	"I'm going to inject you with a small quantity of a substance that causes some itch in most people."	Some itch sensation and wheal and flare	Nocebo-like control II
3	Histamine	"I'm going to inject you with a small quantity of a substance that causes an enormous itch in most people."	A more intense itch and a more extended flare and wheal skin reaction; males > females	Nocebo-like effect II
4	NaCl	"I'm going to inject you with a small quantity of a substance that causes an enormous itch in most people."	Some itch sensation and wheal and flare; males > females	Nocebo-like effect I

To determine whether the sex of the investigator and/or the sex of the participant influence the differences in itch ratings and skin reactions between the control and corresponding nocebo-like conditions (for NaCl and histamine, respectively), non-parametric Mann–Whitney *U* tests were performed, first comparing male with female participants, and secondly comparing participants' reactions to male or female investigators. After correction for multiple comparisons according to the Benjamini-Hochberg procedure we only found flares of greater extent for female investigators in the difference of nocebo-like control and experimental condition II (histamine + exaggerated verbal instruction) ($p = 0.003$). The results are shown in Table SI[1].

DISCUSSION

To our knowledge this is the first study to examine sex-specific differences in perception of experimentally (histamine)-induced pruritus and skin reactions following verbal suggestions raising expectations of marked negative effects from the prick test, taking into account the investigator's and participant's sex.

The participants reported higher itch intensity under nocebo-like experimental conditions I and II (with exaggerated verbal instruction) than under the corresponding control conditions. The higher itch intensity rating was accompanied by enhanced skin reactions in NaCl and histamine conditions and unpleasantness ratings only in nocebo-like condition I (NaCl).

The magnitude of these differences was not significantly different between male and female participants. Thus, we conclude that itch perception and even skin reactions can be induced and intensified by verbal suggestions and instructions, but we found no conclusive evidence for an influence of the sex of the participant.

Different itch intensity ratings and skin reactions of the whole sample

In line with our hypotheses, it was possible to provoke itch sensations and even cutaneous reactions (wheal) by suggestion alone; these were reported to be greater under NaCl prick test + exaggerated verbal instruction compared with those under NaCl prick test (nocebo-like control condition I). Furthermore, itch perception under histamine was enhanced by catastrophizing suggestions; greater values were assigned to itch perception under nocebo-like experimental compared with nocebo-like control condition II.

This is in line with other studies, which show that placebo and nocebo effects can be provoked by verbal suggestions, learning processes (27), expectancy and patient-clinician communication (28). The study of Lang et al. (29) showed that statements with negative emotional content increased anxiety and pain in patients compared with neutral or positive comments. However, the effect may be influenced not only by the expectation of an adverse event, but also by prior learning experience. Colloca & Benedetti (30) reported that patients benefitted more from placebo drugs when they had previously had good positive experiences with the corresponding verum medication. Although our study tested for nocebo, not placebo, effects, one could hypothesize that since the participants in our study experienced the itch sensation on application of histamine solution under the nocebo-like control condition, it should not be surprising that the verbal suggestion "I'm going to inject you with a small quantity of a substance that causes an enormous itch in most people" before a prick test with NaCl solution (nocebo-like experimental condition I) was sufficient to provoke some itch, probably due to expectation. This result is in agreement with the studies of Benedetti et al. (31, 32), in which an increase in pain could also be provoked by suggestions raising expectations of pain while injecting a saline solution. The authors explained this phenomenon by the provocation of expectation-anxiety. Furthermore, several nocebo studies have reported on the modulatory role of endogenous opioids (32, 33). It is known that pruritus can be provoked by opioids (34). Thus, it might be possible that expectation-anxiety leads to opioid release, which is responsible for the observed itch.

Surprisingly, even though we observed an increase in itch intensity under experimental nocebo-like conditions I and II as well as an increase in unpleasantness under nocebo-like condition I, there were no differences in the desire to scratch. Several

[1]https://doi.org/10.2340/00015555-2336

Table II. *Comparison of control and nocebo-like conditions for the whole sample by non-parametric Wilcoxon signed-rank test, corrected for multiple testing by Benjamini & Hochberg procedure (26)*

Control condition	Median (IQR)	Condition	Median (IQR)	Z	*p*-value
Nocebo-like control I		*Nocebo-like effect I*			
Extent of flare (cm)	0 (0–0)	Extent of flare (cm)	0 (0–0)	–0.988	0.323
Extent of wheal (cm)	0.15 (0–0.25)	Extent of wheal (cm)	0.2 (0–0.3)	–3.363	**0.001**
Intensity	0 (0–1)	Intensity	0 (0–1.38)	–2.943	**0.003**
Urge to scratch	0 (0–0)	Urge to scratch	0 (0–0)	–1.602	0.109
Unpleasantness	0 (0–0)	Unpleasantness	0 (0–1)	–2.993	**0.003**
Nocebo-like control II		*Nocebo-like effect II*			
Extent of flare (cm)	5.1 (4.5–6)	Extent of flare (cm)	5.5 (4.53–6.15)	–2.333	**0.02**
Extent of wheal (cm)	1.1 (.95–1.35)	Extent of wheal (cm)	1.1 (1–1.39)	–1.747	0.081
Intensity	4 (2–5)	Intensity	4 (3–6)	–2.678	**0.007**
Urge to scratch	3.5 (1–6)	Urge to scratch	4 (1.25–5)	–0.335	0.737
Unpleasantness	3 (2–5)	Unpleasantness	4 (2–5)	–1.496	0.135

Significant *p*-values in **bold**. IQR: interquartile range.

brain-imaging studies (35–38) have demonstrated activation of the anterior cingulate cortex, prefrontal cortex and insula during anticipation of pain. These brain regions are important for the integration and emotional evaluation of sensory information, but not for motor reactions. Whether these brain regions are also active in the anticipation of itch is unclear. Napadow et al. (39) found activation of the caudate and dorsolateral prefrontal cortex and of the intraparietal sulcus in patients with atopic dermatitis during a nocebo condition in an fMRI study. These regions are responsible for cognitive executive and motivational processing, but not for motor responses. Thus, one might hypothesize that, during anticipation of itch (during nocebo-like conditions), no activation of motor brain regions occurs. This might explain why the desire to scratch remained unchanged under these conditions in our study.

Besides the increased intensity under nocebo-like conditions, we also found enhanced skin reactions to the experimental stimulus in nocebo-like condition I (wheal) and nocebo-like condition II (flare diameter). It can be concluded that this, not only the perception of itch, but also the skin reaction itself, can be influenced by negative verbal suggestions. As already mentioned, anxiety plays an important role in the nocebo response in pain studies. A similar result could be found in itch studies. Kiecolt-Glaser et al. (22) reported that the histamine wheal in patients with allergic rhinitis increased when the subjects were stressed. Anxiety also enhanced the effects of stress. In contrast, Kimata (23) did not find increased histamine flare after stress in patients with atopic dermatitis. One possible explanation for these conflicting results is that patients with atopic dermatitis are already chronically stressed in general because of their skin disease, in contrast to patients with allergic rhinitis or to the healthy volunteers in our sample.

Sex-specific differences in itch intensity ratings and skin reactions

After the correction for multiple testing we only found significant differences in flare size for female and male investigators concerning the differences between the control and the experimental nocebo condition II. Although the results were contradictory concerning the details, the pain studies of Vigil et al. (7), Aslaksen et al. (5) and Kallai et al. (6) all found an influence of the sex of the participant and/or the investigator on ratings of pain intensity. The studies of Klosterhalfen et al. (15, 16) also described different reactions in nausea experiments; females were more prone to habituation, and males to suggestion. While in conflict with these studies, the results of our study (no differences in itch intensity ratings) are in agreement with the systematic review by Horing et al. (9), which analysed 15 articles concerning predictors of placebo response without finding any significance for sex.

Interestingly, the current study found that a more pronounced skin reaction was provoked by female investigators, with regard to the differences between the exaggerated verbal instructions and the control condition in nocebo-like condition II. Kiecolt-Glaser et al. (22) found that histamine wheal increases when subjects are stressed. Anxiety also enhanced the effects of stress. It is likely that in our study the female investigator induced more stress than the male investigator in this condition. As ours is the first study on sex and experimentally induced itch we can only hypothesize about our results. It is possible that itch perception is indeed highly suggestible (11, 12), but that sex plays only a minor role compared with other individual factors.

Study limitations

The current study was performed by one male and one female investigator, thus it cannot be excluded that individual factors influenced the results, masking any sex-specific differences. Using several investigators would exclude the influence of individual factors.

The 4 sub-experiment runs were always performed in the same order (Table I). In an unpublished pilot study ($n = 34$) nocebo condition I (NaCl + exaggerated verbal instruction) was performed first, followed by nocebo condition II (histamine + exaggerated verbal instruction). The participants in this pilot study reported that they evaluated nocebo condition II (histamine) as less intense because the itch intensity of nocebo condition I (NaCl) did not fit the verbal instructions. This indicates a certain learning effect. In the present study the run order was changed to first histamine + exaggerated verbal instruction (3: run, nocebo condition II), followed by NaCl + exaggerated verbal instruction (4: run, nocebo condition I). Randomization of the order of the conditions would have increased the validity of the results, since the order may have influenced the results in the direction that perception of nocebo condition I might have been enhanced due to a learning effect.

Conclusion

Itch perception, and even skin reactions, can be induced and intensified by catastrophizing suggestions and instructions. Sex differences may play only a minor role in nocebo-induced itch perception.

ACKNOWLEDGEMENTS

This study was supported by the gender equality funds of the Medical Faculty of the University Münster [14-006] and by the Open Access Publication Fund of University of Münster.

The authors would like to thank Dr rer. nat. Matthias Borowski from the Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany for statistical support.

The authors declare no conflicts of interest.

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