ORIGINAL ARTICLE   SKIN AND EYE DISEASES

The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients

V. Napadow[1,2], A. Li[1], M.L. Loggia[1], J. Kim[1], I. Mawla[1], G. Desbordes[1], P. C. Schalock[3], E. A. Lerner[3], T. N. Tran[3], J. Ring[4], B. R. Rosen[1], T. J. Kaptchuk[5] & F. Pfab[1,4,6]

[1]Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA; [2]Department of Radiology, Logan University, Chesterfield, MO; [3]Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Dermatology and Allergy, Technische Universität München, Munich, Germany; [5]Program in Placebo Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [6]Department of Prevention and Sports Medicine, Technische Universität München, Munich, Germany

Abstract

Background: Psychological factors are known to significantly modulate itch in patients suffering from chronic itch. Itch is also highly susceptible to both placebo and nocebo (negative placebo) effects. Brain activity likely supports nocebo-induced itch, but is currently unknown.

Methods: We collected functional MRI (fMRI) data from atopic dermatitis (AD) patients, in a within-subject design, and contrast brain response to nocebo saline understood to be allergen *vs* open-label saline control. Exploratory analyses compared results to real allergen itch response and placebo responsiveness, evaluated in the same patients.

Results: Nocebo saline produced greater itch than open saline control ($P < 0.01$). Compared to open saline, nocebo saline demonstrated greater fMRI response in caudate, dorsolateral prefrontal cortex (dlPFC), and intraparietal sulcus (iPS) – brain regions important for cognitive executive and motivational processing. Exploratory analyses found that subjects with greater dlPFC and caudate activation to nocebo-induced itch also demonstrated greater dlPFC and caudate activation, respectively, for real allergen itch. Subjects reporting greater nocebo-induced itch also demonstrated greater placebo reduction of allergen-evoked itch, suggesting increased generalized modulation of itch perception.

Conclusions: Our study demonstrates the capacity of nocebo saline to mimic both the sensory and neural effects of real allergens and provides an insight to the brain mechanisms supporting nocebo-induced itch in AD, thus aiding our understanding of the role that expectations and other psychological factors play in modulating itch perception in chronic itch patients.

Itch is an aversive sensory experience associated with the urge to scratch. It is the cardinal symptom of multiple allergic and dermatological diseases and is known to be significantly modulated by cognitive and emotional factors (1). For instance, placebo and nocebo (negative placebo) effects for itch have been demonstrated in healthy subjects and may be even more pronounced than placebo and nocebo effects for pain (2). Nocebo effects also extend to patients suffering from chronic itch, for example, atopic dermatitis (AD). A previous study found that AD patients receiving histamine reported greater itch when the stimulus was accompanied by negative verbal suggestions about skin response and itch perception (3). Interestingly, itch can be induced without any pruritogenic agent. Recent studies have found that a lecture about itch induced more frequent scratching bouts than a lecture on a neutral topic (4), while visual cues (e.g., scratching videos) can also induce a 'social contagion' itch sensation, which is greater in AD (5), and is associated with functional MRI (fMRI) activity in prefrontal, premotor, somatosensory, and insular brain regions (6). While these studies demonstrate that itch is highly modulated and even evoked by psychological factors, the brain circuitry

supporting clinically relevant forms of nocebo-induced itch perception is unknown.

Nocebo effects are broadly defined as subjective reports of an aversive symptom following administration of an inert stimulus (7, 8) and can be quite powerful. For instance, while placebo responses can be learned from multiple conditioning trials, nocebo responses have been shown to require only a single conditioning trial (9). The brain circuitry supporting nocebo may also be distinct from the circuitry associated with placebo effects (10–12), or may result from an opposite response of identical neurochemical systems (13). Past nocebo neuroimaging studies have mainly investigated nocebo effects in the context of pain; similar approaches to evaluate the brain activity underlying nocebo-induced (or 'pruricebo' (5)) itch are lacking.

In this study, we applied fMRI and our validated temperature-modulation itch model to evaluate the underlying brain circuitry supporting clinically relevant nocebo-induced itch in AD subjects. In separate scans, subjects experienced saline skin prick stimulation under two different conditions – nocebo saline understood to be allergen and an open-label saline control. We hypothesized that subjects would experience significantly greater itch perception under nocebo compared to open saline and that brain response to nocebo-induced itch would be significantly more robust. As the AD patients in this study also completed a separate study where brain response to real allergen itch and placebo responsiveness were assessed (14), separate exploratory analyses correlated (i) nocebo saline vs real allergen brain responses, and (ii) nocebo vs placebo psychophysical outcomes.

Methods

Subjects

Subjects with a clinical diagnosis of AD were enrolled in the study. Inclusion criteria included (i) male or female adults aged 18–60, (ii) AD diagnosis with a SCORAD (SCORing Atopic Dermatitis) score >18, and (iii) type I sensitivity to grass pollen, birch pollen, and/or *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* with wheal and flare formation upon skin prick testing. Patients stopped any immunosuppressive medications (e.g., prednisone, cyclosporine) at least 10 days prior to the study to avoid potential suppression of itch perception. AD patients were recruited by print and email advertisement, as well as through physician colleagues in the Department of Dermatology at Massachusetts General Hospital (MGH). All patients gave informed consent, and the protocol was approved by the Human Research Committee of MGH.

Fourteen patients (8F, age: 25.4 ± 9.1 years, SCORAD: 38.7 ± 14.9, $\mu \pm \Sigma\Delta$) were enrolled in the study.

Experimental protocol and itch provocation model

Subjects first completed a training session and were evaluated with a focused history, physical examination, and real allergen skin prick testing to confirm eligibility by a dermatologist and allergologist (FP). The allergens used to elicit itch were concentrated solutions of grass pollen ($N = 8$), *Dermatophagoides pteronyssinus* (European house dust mite, $N = 3$), or *Dermatophagoides farinae* (American house dust mite, $N = 3$). Handedness was assessed with the Edinburgh Inventory (15). All but one patient was right-handed.

As a part of this training session, subjects experienced how cooling the skin can aggravate real allergen itch perception using our temperature-modulated itch provocation model, which has been previously validated by us (14, 16, 17) and by others (18). Subjects also completed an itch expectancy visual analog scale, which asked subjects to rate the intensity of itch they expect to feel at the MRI in response to allergen testing (anchors: 'no itch' and 'maximum itch').

During the MRI session, AD patients experienced two different temperature-modulation fMRI scan runs with saline. For these runs, a clear and odorless saline solution was placed on the left volar forearm skin (unaffected by any AD lesion), followed by deposition of the solution to the dermal/epidermal junction using a plastic MR-compatible skin prick device (Duotip Test II; Lincoln Diagnostics, Decatur, IL, USA). For the 'open' saline control fMRI run, subjects were instructed that the solution was a 'simple drop of water, which we are using as a control condition to compare with the drop of allergen you will receive later'. For the 'nocebo' saline fMRI run, this instruction was not given when the drop of saline was deposited into the skin. Subjects were clearly led to expect an allergen solution prick test at this scan, as they had experienced this identical ritual at previous study visits on different days (14). The order of these two saline scan runs was counterbalanced. For both fMRI scans, 120 s after skin prick procedures, the saline solution was wiped away with a sterile cellulose pad. A 30×30 mm sized MRI-compatible probe (Medoc Advanced Medical Systems, Ramat Yishai, Israel) was then placed on the solution-treated skin area for temperature modulation during subsequent fMRI scanning.

Following the scan runs, subjects used a numerical rating scale from 0 (no itch) to 100 (most intense itch imaginable) to rate the intensity of itch experienced separately during neutral and cool temperature-modulation blocks. As in our previous studies (14, 16, 17, 19–22), subjects were instructed that a rating of 33 corresponds to an 'urge to scratch' threshold. Above this threshold, each individual feels the clear-cut desire to scratch, which, however, was not permitted (and confirmed by observation).

Psychophysical analyses

Itch severity was rated for neutral and cool blocks following the fMRI scan. Itch intensities for the cool temperature block (more severe itch) were assessed for normality using the Shapiro–Wilk normality test and compared between the nocebo saline and open saline control, using a paired Student's *t*-test or Wilcoxon signed-rank test, depending on normality. Results from psychophysical analyses were significant at $P < 0.05$.

MRI scanning protocol

Imaging was performed at 3-tesla on a Siemens Trio MRI scanner (Siemens AG, Erlangen, Germany). High-resolution T1-weighted structural imaging was completed with an isotropic multi-echo MPRAGE pulse sequence (TR/TE1/TI = 2530/1.64/1200 mS, matrix = 256 × 256, FOV = 256 mm, FA = 7°). Functional MRI data were collected with a gradient echo T2*-weighted pulse sequence (TR/TE = 2 s/30 ms, 32 AC-PC aligned slices, slice thickness = 3.6 mm, matrix = 64 × 64, FOV = 200 mm, FA = 90°) and a 32-channel multi-array coil. All block design fMRI scan runs included eight equal 20-s cycles, consisting of alternating neutral (32°C) and cool (25°C) temperature blocks (1.5-s transit time between temperatures), resulting in a total 180 time points over a 6-min scan run. Skin temperature over the solution deposition site was modulated by the Medoc thermal stimulator.

FMRI data analyses

BOLD images were preprocessed using the FMRIB Software Library (FSL) and tools available through the FreeSurfer software package (23, 24). Data were skull-stripped (brain extraction tool [BET]) (25), slice-timing-corrected, motion-corrected (MCFLIRT) (26), and spatially smoothed with a FWHM 5-mm Gaussian kernel (27). Data were excluded if gross translational motion exceeded 3 mm on any axis, or if relative motion spikes exceeded 1.5 mm. Data were high-pass filtered (f_{high} = 0.017 Hz) and analyzed with a general linear model (GLM). This GLM used three regressors based on previously described dynamics of temperature-modulated itch sensation (14, 16, 22, 28). A block regressor over the first half of cool temperature blocks captured a period of increasing itch. A regressor over the second half of cool blocks captured a peak-plateau itch period. Finally, a regressor of no-interest covered the first 12 s of the 20-s neutral (32°C) block, when itch sensation decreases to its nadir. Importantly, as temperature modulation was a component of all scans, our analysis applied to both nocebo and control open saline fMRI scans, thus controlling for brain activity related to the relatively mild temperature change.

To aid group analysis, cortical surface reconstruction was performed using FreeSurfer for structural–functional boundary-based coregistration (29). GLM parameter estimates and their variances were passed up to the group level using registration to standard Montreal Neurological Institute (MNI) space (FMRIB's Nonlinear Image Registration Tool [FNIRT], FSL). A mixed-effects model contrasted brain response between the open and nocebo saline fMRI scans (FMRI Expert Analysis Tool [FEAT], FSL). Results for both increasing and peak itch regressors were cluster-corrected for multiple comparisons (cluster forming threshold: $z > 2.3$, corrected threshold: $P < 0.05$).

Exploratory analyses

Two separate exploratory analyses were conducted. The first compared brain response to nocebo itch with previously reported real allergen itch data collected from separate scan runs from the same AD subjects (14). The methods for the real allergen scan run were identical to those of the nocebo scan, except that real allergen (and not saline) was deposited on the skin surface prior to scanning. Correlations between nocebo (relative to control) brain response *vs* brain response in the same regions to allergen-evoked itch were computed, using the percent-signal change from the group cluster maximum voxel.

The second exploratory analysis correlated behavioral data on previously reported (14) placebo intervention responsiveness (see Appendix S1) with nocebo responsiveness from the same patients.

Results

Psychophysical results

Itch was elicited by saline prick testing and was significantly greater during cool blocks compared to neutral blocks for both open and nocebo conditions (Fig. 1, Table S1, nocebo: cool = 37.0 ± 20.6, neutral = 27.9 ± 19.1, $P < 0.005$; control open saline: cool = 18.5 ± 18.7, $\mu \pm \Sigma D$; neutral = 10.5 ± 11.6, $P < 0.05$). Greater itch during cool blocks is consistent with previous studies using the temperature-modulated allergen itch model, now utilized by other research groups as well (18), and suggests similar temporal dynamics for itch perception between nocebo and real allergen. Notably, while both the nocebo and control open conditions found, on average, greater itch during cool blocks, only the nocebo condition produced cool block itch of moderate intensity, >33/100 (i.e., 'desire to scratch' threshold). While the nocebo itch data were normally distributed (nocebo: $W = 0.95$, $P = 0.05$ threshold = 0.87), the open saline data were not ($W = 0.85$). Hence, a nonparametric paired Wilcoxon signed-rank test was used to demonstrate that the nocebo condition produced significantly greater itch compared to the open saline condition ($Z = -3.18$, $P < 0.01$). There were no order effects for open saline control itch (nocebo 1st: 21.8 ± 13.6; open 1st: 16.0 ± 22.2, $\mu \pm \Sigma\Delta$, $\pi > 0.5$) or for the difference between nocebo-induced itch and open saline itch (nocebo 1st: 15.6 ± 15.9; open 1st: 20.6 ± 13.8, $\mu \pm \Sigma\Delta$, $\pi > 0.5$), suggesting that nocebo-induced itch sensation did not persist into subsequent open saline itch fMRI scans.

We also evaluated how expectancy for itch was associated with nocebo itch ratings and found a trending correlation between itch expectancy ratings and nocebo (minus open saline) itch ratings ($r = 0.47$, $P = 0.1$).

FMRI results

We found that compared to open saline, nocebo-induced itch produced greater fMRI signal increase during the increasing itch phase in the dorsolateral prefrontal cortex (dlPFC), caudate, and intraparietal sulcus (iPS) (Fig. 2, Table 1). No regions demonstrated greater activation to open saline compared to nocebo-induced itch. Also, no differences between nocebo and open saline were found for the peak itch phase.
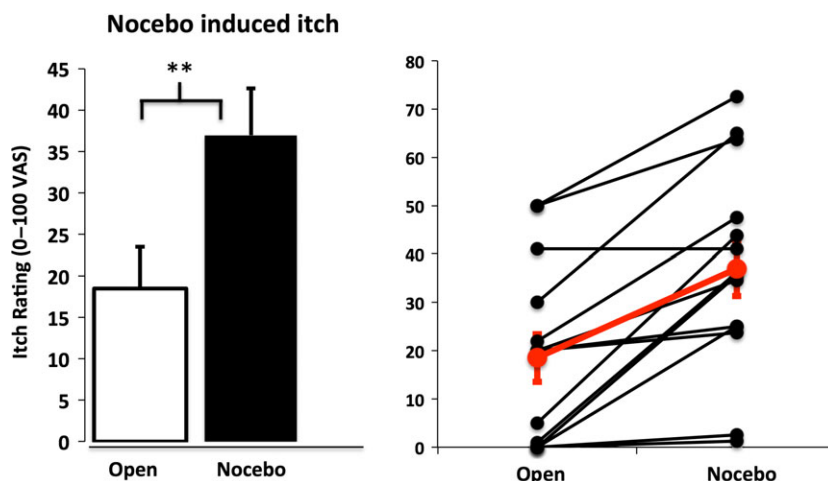
Figure 1 Nocebo saline produced greater itch compared to open saline control. **$P < 0.01$. Itch ratings reported for cool temperature blocks, when ratings were greatest for all conditions. Error bars denote SEM.
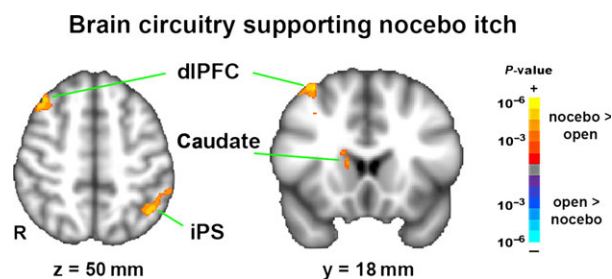
Figure 2 Compared to open saline control, nocebo-induced itch produced greater functional MRI (fMRI) signal increase in the dorsolateral prefrontal cortex (dlPFC), caudate, and intraparietal sulcus (iPS). This differential brain response was found for the increasing itch phase.

Exploratory analyses

Exploratory analyses compared nocebo itch brain response to real allergen itch response. Conjunction analysis demonstrated common clusters within the right dlPFC and right caudate shared by nocebo-induced increasing-phase itch and real allergen peak-phase itch (Fig. 3). In addition, nocebo (relative to control) caudate response during increasing itch was correlated ($r = 0.58$, $P < 0.05$) with caudate ($x = -20$ mm, $y = 10$ mm, $z = 16$ mm) response to real allergen during increasing itch (Fig. 3). Moreover, nocebo (relative to control) dlPFC response during increasing itch was correlated ($r = 0.61$, $P < 0.05$) with dlPFC ($x = 36$ mm, $y = 20$ mm, $z = 52$ mm) response to real allergen during the peak-plateau phase (note that dlPFC was not activated by real allergen during *increasing* itch (14)). While real allergen activated superior parietal lobule during the peak itch phase, this activation was not correlated with iPS activation by nocebo-induced itch ($r = -0.14$, $P = 0.63$).

In addition, we also compared ratings for nocebo and placebo responsiveness in the same AD patients. While placebo did not significantly reduce allergen-evoked cool block itch ratings ($\Delta_{post-pre} = 1.8 \pm 16.7$, $P > 0.5$), significant within-group heterogeneity provided sufficient dynamic range for cross-correlation with nocebo responsiveness in the same subjects. We found a significant correlation between nocebo-induced itch ratings (ratings following nocebo saline) and the change in itch ratings (for allergen-evoked itch) following a placebo intervention (Fig. 4, $r = -0.59$, $P < 0.05$). Thus, subjects who rated greater itch sensations following nocebo saline administration also reported greater improvement (post–pre) in allergen-evoked itch ratings following placebo intervention.

There was no association between nocebo ratings and duration of AD, SCORAD score, or age (all at $P > 0.05$, Table S2), while sex also did not differentiate nocebo response (unpaired t-test, $P = 0.27$).

Discussion

Our results demonstrated that nocebo-induced itch produced greater itch sensation compared to a control open saline provocation in patients suffering from AD. FMRI data showed that compared to control, brain response to nocebo-induced itch showed greater fMRI signal increase in brain regions important for motivational, attention, and cognitive processing, including caudate, dlPFC, and iPS (Fig. 5). An exploratory analysis showed that real allergen provocation in these same AD patients produced activation in similar areas, including the striatum and dlPFC. In fact, brain response to real allergen was correlated with nocebo-induced itch response in some of these same brain regions—that is, subjects with greater dlPFC and caudate activation to real allergen also had greater dlPFC and caudate activation, respectively, for nocebo-induced itch. These results suggest that when subjects perceive nocebo-induced itch, the prefrontal and striatal circuitry activated by real allergen is also activated to support this nocebo-induced itch sensation.

Table 1 Brain areas supporting nocebo-induced itch in atopic dermatitis (AD) patients

Side		Size (mm³)	Location (MNI)			Nocebo % change	Open % change	Z-score
			X	Y	Z			
Increasing phase itch								
Nocebo > open saline								
Dorsolateral prefrontal cortex	R	4008	36	22	54	0.17 ± 0.31	−0.43 ± 0.48	4.11
Intraparietal sulcus	L	4064	−50	−46	42	0.19 ± 0.30	−0.17 ± 0.22	4.22
Caudate	R	3720	14	18	10	0.16 ± 0.19	−0.07 ± 0.20	2.77
Open saline > nocebo								
None								
Peak-plateau phase itch								
None								
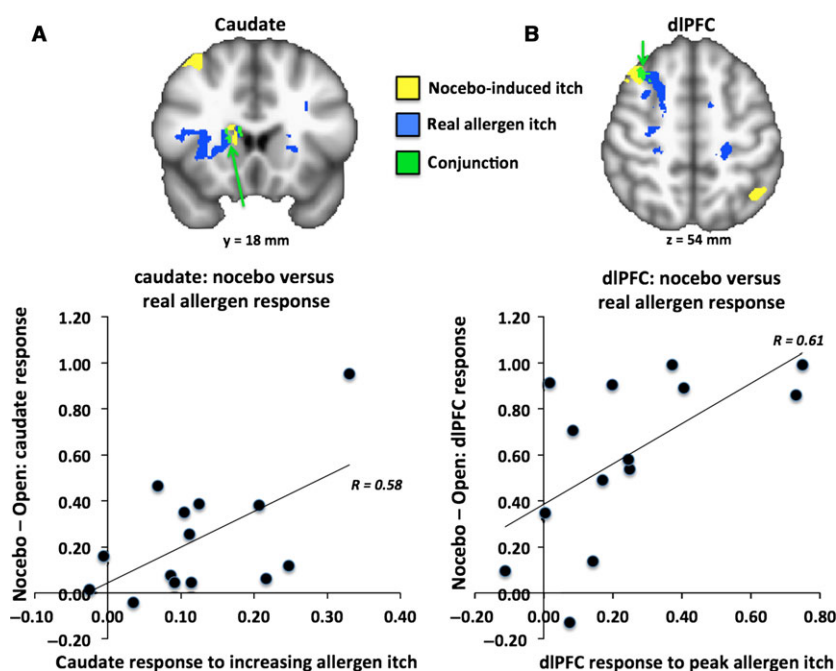
Figure 3 A conjunction analysis found significant overlap between brain response to nocebo-induced itch and allergen itch in the (A) caudate and (B) dlPFC. In fact, subjects with greater dlPFC (peak itch phase) and caudate (increasing itch phase) activation to real allergen also had greater dlPFC ($r = 0.61$, $P < 0.05$) and caudate ($r = 0.58$, $P < 0.05$) activation, respectively, for increasing nocebo-induced itch.
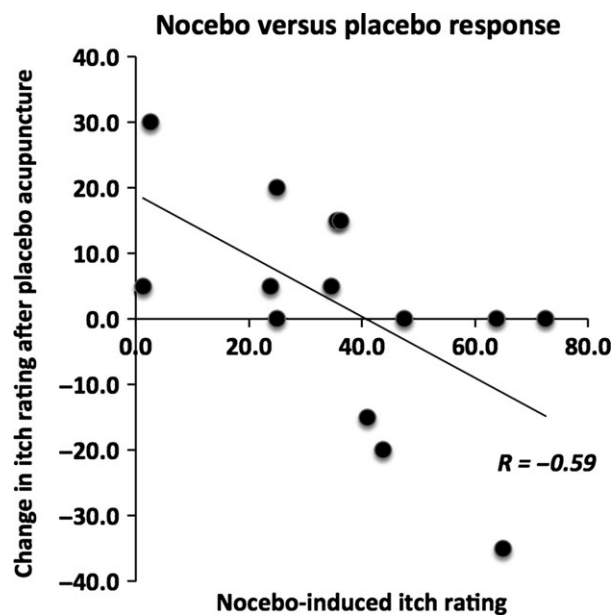
Finally, another exploratory analysis showed that subjects reporting greater nocebo-induced itch also demonstrated greater reduction of allergen itch ratings following a placebo intervention, suggesting increased generalized modulation of itch perception in these subjects. Our study identifies the brain circuitry supporting imagined itch in AD and demonstrates the capacity of nocebo saline to mimic the effect of real allergens in chronic AD patients characterized by central sensitization for itch (30).

The dlPFC and caudate were found to be the key brain regions supporting both real allergen and nocebo-induced itch. Previous neuroimaging studies have noted that nocebo interventions upregulate fMRI response to aversive stimuli

(i.e., pain) within core pain-processing areas such as insula/somatosensory cortex (31) or even spinal dorsal horn (32). The dlPFC is also an important pain modulatory region that has been reported to exert active control over pain perception by mediating cortico-cortical and cortico-subcortical interactions (33). On the other hand, the caudate, a subregion of the striatum, receives inputs from the cortex and plays a critical integrative role in striato-thalamo-cortical circuits implicated in motivational processing. This circuitry has been found to be dysregulated in pathology related to generalized urge suppression (34). Examples of such disorders include obsessive/compulsive disorder, obesity, and addiction, and in the case of chronic itch, striato-thalamo-cortical circuits

likely support the urge to scratch (35). Hence, the dlPFC region noted in our analysis may underlie the cognitive executive process by which a verbal suggestion ('skin prick test again') coupled with an innocuous sensory input (neutral to cool transition in our study) is perceived as an aversive sensation (nocebo-induced itch) learned/conditioned over multiple previous real allergen sessions with identical context, thereby releasing activity of a striatal motor urge circuitry. In fact, this combination of verbal suggestion and conditioning has recently been shown to be necessary in producing an itch nocebo effect (36).

We previously identified phase-variant brain response to pruritogenic afference evoked by real allergen in these same
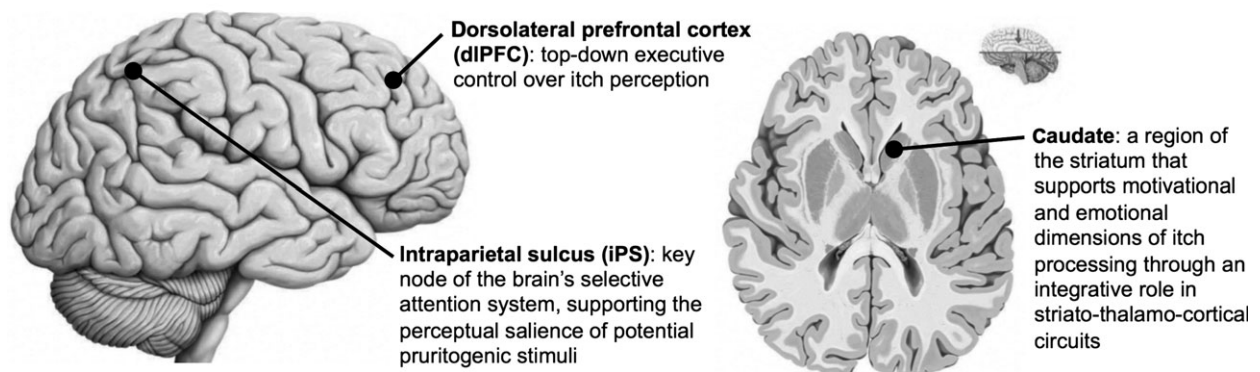

Figure 4 Atopic dermatitis (AD) patients reporting greater nocebo-induced itch also demonstrated greater reduction of allergen itch ratings following a placebo intervention ($r = -0.59$, $P < 0.05$), suggesting increased capacity for generalized modulation of itch perception in these subjects.

AD patients (14). Increasing itch was associated with activation in the insula, anterior mid-cingulate cortex, striatum, and ventrolateral prefrontal cortex. In contrast, peak-plateau itch activation was noted in the dlPFC, premotor, and superior parietal lobule regions, that is, higher cognitive and attention modulation regions that likely contextualize the stimulus. Interestingly, while our previous study showed that allergen itch produced caudate activation during early increasing itch and dlPFC activation during late peak-plateau itch, nocebo-induced itch was instead associated with *both* caudate and dlPFC activation during increasing itch. Hence, while the function of the dlPFC in processing bottom-up allergen itch may be to contextualize and reappraise the sensation after initial striatal activity, for top-down-mediated nocebo-induced itch, the dlPFC, together with the caudate, may instead serve to initiate itch sensation following a now-conditioned temperature transition stimulus, given that subjects had been familiarized to allergen itch over prior sessions, setting up a conditioned response to the prick testing intervention. This phenomenon may be clinically relevant, as AD patients might show propensity to itch perception in response to neutral or noxious (but not innately pruritogenic) stimuli by activating similar circuitry.

We also found that iPS showed greater fMRI signal increase during nocebo-induced itch compared to control open saline. The iPS is known to be a key node of the brain's selective attention system, and more recent studies have suggested that the iPS is particularly related to the perceptual salience of the attended stimulus (37). This latter function is consistent with how the brain might respond toward a potentially itch-inducing stimulus when the expectation for itch is greater, leading to greater saliency of somatosensory stimulus change (i.e., transition from a neutral to a cool temperature). Interestingly, the dlPFC and iPS clusters supporting nocebo-induced itch were both localized to portions of the frontoparietal control network (38, 39), as identified from prior large-scale resting state connectivity analyses (40). This network is known to support cognitive/executive control over sensory perception and decision-making processing. Thus,

Overview of brain regions supporting nocebo itch

Figure 5 An overview of brain regions identified in our study as supporting nocebo itch.

nocebo-induced itch perception may be mediated by executive frontoparietal control over subcortical striatal brain regions (e.g., caudate) that encode the motivational and emotional dimensions of this aversive sensation.

An exploratory analysis also found an association between subjects reporting greater nocebo-induced itch and those reporting greater reduction of allergen itch ratings following a placebo intervention, suggesting increased capacity for generalized modulation of itch perception in these subjects. The association between nocebo and placebo effects has not been well studied. While some pain studies suggest that the brain circuitry supporting nocebo involves limbic (e.g., hippocampus) brain activity and is distinct from the circuitry associated with placebo effects (10, 12, 41), other studies have shown that nocebo/placebo effects occur via opposite responses of the same neurochemical systems (13). Similarly, a recent study found that placebo manipulations produce analgesia and hyperhedonia via shared affective neurocircuitry, which targets early sensory processing (42), a finding that may relate to our observation that nocebo itch was engaged through cortico-striatal activity during an early increasing itch phase. However, much more research is needed to better understand the relation between placebo and nocebo responders for itch.

The role of anxiety, as well as more general constructs such as stress and negative affect, has been highly touted in previous studies of nocebo-induced pain. Anxiety is thought to arise from negative expectation, and prior studies have shown that negative suggestions modulate expectations and heighten anxiety leading to greater pain report and hyperactivation in prefrontal and limbic brain regions thought to process cognitive and affective dimensions of pain (12, 43). In our case, previous experience with the allergen prick test induces expectation for itch when exposed to liquid pricked into the skin, and a trend was found between expected and nocebo itch intensity.

While we did not include a healthy controls in this study, a previous neuroimaging study (44) demonstrated that brain response to identical pruritogenic substances (e.g., histamine) is different between AD and healthy controls with AD showing greater activation in thalamus, caudate, and pallidum. Such differences may extend to differences in brain circuitries supporting nocebo itch as well.

Limitations include the fact that temporal evolution of nocebo itch is not as well understood as allergen itch. However, itch psychophysics were similar for temperature effects (i.e., greater itch during cool blocks), and while more

research is needed, we chose a similar GLM to enhance comparability between studies.

In conclusion, our study provides a better understanding of the brain mechanisms supporting nocebo-induced itch in AD patients, which will aid our understanding of the role that expectations and other psychological factors play in worsening and improvement of itch perception in chronic itch patients.

Acknowledgments

Conflict of interests

The authors declare that they have no conflict of interests.

Author contributions

VN and FP involved in project conception, experimental design, data collection, data analysis, data interpretation, and manuscript preparation; AL involved in data collection, data analysis, data interpretation, and manuscript preparation; ML involved in experimental design, data collection, data interpretation, and manuscript preparation; JK, IM, GD, EL, TT, JR, and BR involved in data interpretation and manuscript preparation; PS involved in experimental design, data interpretation, and manuscript preparation; TK involved in project conception, experimental design, data interpretation, and manuscript preparation. All authors have read and approved the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Detailed procedures for placebo administration.

Table S1. Summary of psychophysical results of itch.

Table S2. Nocebo itch rating correlations.

References

1. Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus. *N Engl J Med* 2013;**368**:1625–1634.

2. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain* 2011;**152**:1486–1494.

3. Scholz O, Hermanns N. Illness behavior and cognitions influence the perception of itching

of patients suffering from atopic dermatitis. *Zeitschrift für klinische Psychologie* 1994;**23**:127–135.

4. Niemeier V, Kupfer J, Gieler U. Observations during an Itch-Inducing Lecture. *Dermatol Psychosomat* 2000;**1**:15–18.

5. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of

itch in atopic dermatitis and healthy subjects. *Br J Dermatol* 2011;**164**:1299–1303.

6. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. *Proc Natl Acad Sci USA* 2012;**109**:19816–19821.

7. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and

the nocebo phenomenon. *JAMA* 2002;**287**:622–627.

8. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth* 2012;**12**:22–29.

9. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. *Pain* 2010;**151**:430–439.

10. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J Neurosci* 2006;**26**:12014–12022.

11. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med* 2011;**3**:70ra14.

12. Kong J, Gollub RL, Polich G, Kirsch I, Laviolette P, Vangel M et al. A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. *J Neurosci* 2008;**28**:13354–13362.

13. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008;**65**:220–231.

14. Napadow V, Li A, Loggia ML, Kim J, Schalock PC, Lerner E et al. The brain circuitry mediating antipruritic effects of acupuncture. *Cereb Cortex* 2014;**24**:873–882.

15. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;**9**:97–113.

16. Pfab F, Valet M, Sprenger T, Toelle TR, Athanasiadis GI, Behrendt H et al. Short-term alternating temperature enhances histamine-induced itch: a biphasic stimulus model. *J Invest Dermatol* 2006;**126**:2673–2678.

17. Valet M, Pfab F, Sprenger T, Woller A, Zimmer C, Behrendt H et al. Cerebral processing of histamine-induced itch using short-term alternating temperature modulation–an FMRI study. *J Invest Dermatol* 2008;**128**:426–433.

18. van de Missanga F, Sprenger C, Büchel C. BOLD responses to itch in the human spinal cord. *NeuroImage* 2015;**108**:138–143.

19. Pfab F, Athanasiadis GI, Huss-Marp J, Fuqin J, Heuser B, Cifuentes L et al. Effect of acupuncture on allergen-induced basophil activation in patients with atopic eczema: a pilot trial. *J Altern Complement Med* 2011;**17**:309–314.

20. Pfab F, Hammes M, Backer M, Huss-Marp J, Athanasiadis GI, Tolle TR et al. Preventive effect of acupuncture on histamine-induced itch: a blinded, randomized, placebo-

controlled, crossover trial. *J Allergy Clin Immunol* 2005;**116**:1386–1388.

21. Pfab F, Huss-Marp J, Gatti A, Fuqin J, Athanasiadis GI, Irnich D et al. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema – a blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2010;**65**:903–910.

22. Pfab F, Valet M, Sprenger T, Huss-Marp J, Athanasiadis GI, Baurecht HJ et al. Temperature modulated histamine-itch in lesional and nonlesional skin in atopic eczema – a combined psychophysical and neuroimaging study. *Allergy* 2010;**65**:84–94.

23. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999;**9**:179–194.

24. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage* 1999;**9**:195–207.

25. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;**17**:143–155.

26. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage* 2002;**17**:825–841.

27. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 2004;**23**(Suppl 1): S208–S219.

28. Pfab F, Kirchner MT, Huss-Marp J, Schuster T, Schalock PC, Fuqin J et al. Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis - a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2012;**67**:566–573.

29. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *NeuroImage* 2009;**48**:63–72.

30. Ikoma A, Fartasch M, Heyer G, Miyachi Y, Handwerker H, Schmelz M. Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. *Neurology* 2004;**62**:212–217.

31. Schmid J, Theysohn N, Gass F, Benson S, Gramsch C, Forsting M et al. Neural mechanisms mediating positive and negative treatment expectations in visceral pain: a functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. *Pain* 2013;**154**:2372–2380.

32. Geuter S, Buchel C. Facilitation of pain in the human spinal cord by nocebo treatment. *J Neurosci* 2013;**33**:13784–13790.

33. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003;**126**:1079–1091.

34. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010;**35**:217–238.

35. Leknes SG, Bantick S, Willis CM, Wilkinson JD, Wise RG, Tracey I. Itch and motivation to scratch: an investigation of the central and peripheral correlates of allergen- and histamine-induced itch in humans. *J Neurophysiol* 2007;**97**:415–422.

36. Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Donders AR, van Middendorp H et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One* 2014;**9**:e91727.

37. Geng JJ, Mangun GR. Anterior intraparietal sulcus is sensitive to bottom-up attention driven by stimulus salience. *J Cogn Neurosci* 2009;**21**:1584–1601.

38. Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA et al. Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA* 2007;**104**:11073–11078.

39. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J Neurophysiol* 2008;**100**:3328–3342.

40. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 2011;**106**:1125–1165.

41. Freeman S, Yu R, Egorova N, Chen X, Kirsch I, Claggett B et al. Distinct neural representations of placebo and nocebo effects. *NeuroImage* 2015;**112**:197–207.

42. Ellingsen DM, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H et al. Placebo improves pleasure and pain through opposite modulation of sensory processing. *Proc Natl Acad Sci USA* 2013;**110**:17993–17998.

43. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med* 2010;**16**:1277–1283.

44. Schneider G, Stander S, Burgmer M, Driesch G, Heuft G, Weckesser M. Significant differences in central imaging of histamine-induced itch between atopic dermatitis and healthy subjects. *Eur J Pain* 2008;**12**:834–841.