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Itch and Motivation to Scratch: An Investigation of the Central and Peripheral Correlates of Allergen- and Histamine-Induced Itch in Humans

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Leknes, Siri G., Susanna Bantick, Carolyn M. Willis, John D. Wilkinson, Richard G. Wise, and Irene Tracey. Itch and motivation to scratch: an investigation of the central and peripheral correlates of allergen- and histamine-induced itch in humans. *J Neurophysiol* 97: 415–422, 2007. First published August 16, 2006; doi:10.1152/jn.00070.2006. Intense itch and urge to scratch are the major symptoms of many chronic skin ailments, which are increasingly common. Vicious itch-scratch cycles are readily established and may diminish quality of life for those afflicted. We investigated peripheral and central processing of two types of itch sensation elicited by skin-prick tests of histamine and allergen solutions. Itch-related skin blood flow changes were measured by laser Doppler in 14 subjects responsive to type I allergens and 14 nonatopic subjects. In addition, this study examined central processing of both types of itch using functional magnetic resonance imaging (fMRI). Itch perception and blood flow changes were significantly greater when itch was induced by allergens compared with histamine. Both types of itch correlated significantly with activity in the genua anterior cingulate, striatum, and thalamus. Moreover, itch elicited by allergens activated orbitofrontal, supplementary motor, and posterior parietal areas. Histamine-induced itch also significantly correlated with activation in the insula bilaterally. The identification of limbic and ventral prefrontal activation in two types of itch processing likely reflects the subjects' desire to relieve the itch sensation by scratching, and these regions have been repeatedly associated with motivation processing. A dysfunction of the striato-thalamo-orbitofrontal circuit is believed to underlie the failure to regulate motivational drive in disorders associated with strong urges, e.g., addiction and obsessive compulsive disorder. The patterns of itch-induced activation reported here may help explain why chronic itch sufferers frequently self-harm through uncontrollable itch-scratch cycles.

INTRODUCTION

Itch is typically defined as “an unpleasant sensation leading to a desire to scratch” (Greaves and Khalifa 2004). Like pain, itch is a subjective sensation and may have phylogenetically evolved for a defense purpose (Stante et al. 2005). Chronic itch conditions are increasingly common and represent a significant cost to society (Carroll et al. 2005). Scratching is an important factor in the maintenance of symptoms in chronic itch, and diminish the sufferer's quality of life (Wahlgren 1999). Affected individuals struggle to resist the strong urge to scratch, and a vicious itch-scratch cycle is readily established. This scratching frequently results in tissue injury, thereby constituting conscious self-harming.

Itch sensation can be evoked not only chemically and electrically (Darsow et al. 2000; Ikoma et al. 2005), but also psychologically (Niemeier et al. 2000). Research has traditionally focused on itch induced by histamine, which directly stimulates histamine type 1 receptors on C-pruriceptors (Schmelz et al. 1997). The skin-prick test can be used to deliver chemical substances to the dermo-epidermal junction of the skin, which has the greatest density of histamine receptors (Smith 1992). Outside the laboratory, histamine is the mediator for itch in several conditions, including insect bite reactions (Schmelz 2001). In some individuals, type I allergens such as house dust mite can also elicit intense itch when delivered to the skin with the prick test.

We used the skin-prick test to generate reliable pruritic stimuli from both histamine and allergens in two experiments. First, we examined the wheal and flare reaction in the skin surrounding the prick test site. Blood-flow changes in the microvasculature of the skin were measured using laser Doppler flowmetry (Olsson et al. 1988). Subjects also rated the intensity of the itch sensation continuously. The aim was to establish the temporal profiles of itch perception and blood-flow increases in response to histamine and type I allergens.

In a second experiment, we investigated the central processing of both types of itch by correlating the subjects' itch intensity ratings with the blood-oxygenation-level-dependent (BOLD) response. Previous imaging studies of histamine-induced itch have implicated regions involved in interoceptive and attentional processing, such as the insular, primary and supplementary motor, anterior cingulate, and posterior parietal cortices (Drzezga et al. 2001; Mochizuki et al. 2003).

To date, the neural underpinnings of allergen-induced itch perception have not been examined directly using neuroimaging techniques. We hypothesized that in response to both types of intense itch over a scanning session (>15 min) with no distracting task, subjects would activate areas involved in the processing of the sensory and motivational aspects of bodily emotions, such as the insula, the cingulate cortex, and the striatum. On the basis of the commonalities and divergences we observed with histamine- and allergen-induced itch in the first experiment using laser Doppler flowmetry, we expected similar, but not identical, activation patterns in response to the two types of itch in the brain.

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METHODS

Laser Doppler study

SUBJECTS. Twenty-eight healthy, right-handed adult female subjects were recruited, following approval by the local Research Ethics Committee. Written informed consent was obtained and a medical screen carried out, including allergy testing with a standard battery of type I allergens. 14 subjects (the atopic cohort) displayed prick-test positivity to a type I allergen (20–58 yr, mean: 39 yr, with a history of mucosal atopy to grass pollen and/or house dust mite). Fourteen age-matched subjects (21–57 yr, mean: 40 yr) yielded negative results on prick testing with type I allergens (the nonatopic cohort). No subject had a past or present history of current systemic or skin disease and none were taking medication.

ITCH INDUCTION. Skin-prick testing was performed on the volar aspect of the left forearm using 5- μ l drops of grass pollen (standardized grass pollen extract, 100,000 bioequivalent allergy units/ml, Hollister-Stier Laboratories, Spokane, WA), or house dust mite extracts (standardized mite extract, 30,000 allergy units/ml, Hollister-Stier), histamine (10 mg/ml of histamine dihydrochloride, Bio-Diagnostics, Upton on Severn, Worcestershire, UK), and saline (negative control). Sterile, single-use lancets (Bio-Diagnostics) were used to give a single skin prick through a 5- μ l drop of test substance so as to deliver the substance to the dermo-epidermal junction. Subjects were seated with their left arm resting on a cushion on a chair arm and the other hand operating the visual analog scale (VAS) slider (see following text). The 14 subjects who had responded positively to allergy testing were challenged with their specific allergen, histamine, and a saline control on three consecutive days. The 14 nonatopic subjects were challenged with saline and histamine on two consecutive days. The challenges were conducted in a double-blinded fashion, and the order of application was randomized so as to avoid the effects of expectation. The testing was carried out in the winter months (January to March) to minimize the influence of environmental allergens. Room temperature was maintained at $21 \pm 1^\circ\text{C}$ (mean \pm SD) throughout. All tests were carried out in the proximity of qualified medical staff.

BEHAVIORAL DATA. Subjects rated itch intensity continuously using a slider to move the cursor along a computerized, numerical VAS, where 0 = no itch, 3 = desire to scratch, and 10 = worst itch imaginable. Each subject was allowed a few minutes to familiarize themselves with the rating procedure before the experiment began. Itch intensity was rated for a total of 20 min after the prick test.

LASER DOPPLER FLOWMETRY. We used a DRT4 laser Doppler perfusion monitor system and associated software (Moor Instruments, Axminster, Devon, UK, <http://www.moor.co.uk>), which produces an output signal that is proportional to the blood cell perfusion (or flux). Microvascular perfusion is the product of mean blood cell velocity and mean blood cell concentration present in the small volume of tissue measured under illumination from the laser beam.

The laser Doppler probe was secured on the skin surface before itch induction. A small segment was removed from the laser Doppler probe pad so that the shoulder of the prick test lancet rested 1 cm distal of the probe center, ensuring that measurements were taken from a consistent position within the region of flare. Measurements of blood flow (2 readings/s) and skin temperature were taken for 5 min prior to prick testing and 20 min post-prick testing.

STATISTICAL ANALYSIS. Data points from the laser Doppler system and the continuous VAS ratings were summated within 15-s blocks for ease of data management and analysis. Mean values and SDs were calculated for each cohort and each prick test solution. Grass pollen and house dust mite data were combined to produce the “type I allergen group.” An ANOVA for repeated measurements was carried out using Statistical (Statsoft) software.

Imaging study

SUBJECTS. Sixteen healthy right-handed adult subjects were recruited, after approval by the local Research Ethics Committee. Written informed consent was obtained and a medical screen, including type I allergy testing, carried out prior to the study to determine suitability for the experiment and MRI compatibility. Positive type I allergens were identified for eight subjects with a history of mucosal atopy to grass pollen and/or house dust mite (4 male, 4 female, mean age: 44 ± 3.4 yr; the atopic cohort). One female subject was excluded from further analysis as she reported no itch during the scan. Eight nonatopic subjects (5 male, 3 female, mean age: 34.4 ± 2.3 yr) yielded negative results on prick testing with type I allergens. No subject had a past or present history of current systemic or skin disease, and none were taking medication. All tests were carried out in the proximity of qualified medical staff.

ITCH INDUCTION. Each subject was asked to lie as still as possible in the magnet. The subjects could see the screen through prism glasses and responded with button presses. Itch was induced in the same way as in the laser Doppler experiment, with the following alterations: 1) itch was induced on the skin between the toes of the subject's right foot, which is hairless and easily accessible in the scanner environment; 2) two lancet pricks were made through the same drop of substance as pilot data indicated that this induced a more robust itch sensation; 3) the prick test was made 60 s after the scanning began, thus providing some baseline measurements; 4) as the laser Doppler experiment revealed no effects of interest during the saline control experiment, and no significant differences between groups in response to histamine, atopic subjects were tested only once with their specific allergen. For the nonatopic subjects who were tested with histamine, the same double prick test procedure was repeated at 6 and 11 min. This was because the results from the laser Doppler experiment indicated that perceived itch intensity dropped off more quickly in histamine-induced itch as compared with allergen-induced itch. Pilot studies indicated that itch intensity summates with repeated histamine prick tests, and that repeating the procedure every 5 min yielded a more intense, longer-lasting itch sensation (data not shown).

BEHAVIORAL DATA. A simplified itch VAS rating scale (where 0 = no itch and 5 = worst itch imaginable, this more narrow scale was used because of technical limitations in the scanner environment) was presented on a screen outside the scanner bore for 6 s every 30 s. Subjects could view this screen from their supine position in the scanner via prism glasses. Each subject was allowed a few minutes to familiarize themselves with the rating procedure before the experiment began. Subjects used a button press to rate the itch they felt during the time when the scale was presented. Ratings were obtained every 30 s throughout the experiment. We did not record continuous ratings to avoid motion artifacts in the data. Each subject's mean rated itch intensity after the prick test was computed, and the differences between types of itch were explored using a student's *t*-test. Correlations between mean itch ratings in the two studies were investigated using SPSS.

IMAGE ACQUISITION. Subjects were scanned in a 3 T human MRI scanner (Oxford Magnet Technology, 1-m bore) using a bird-cage radio frequency coil for pulse transmission and signal reception within a reduced bore gradient coil (Magnex SGRAD MK III). A standard whole-brain gradient echo-planar imaging (EPI) sequence was used for functional scans [repetition time (TR) = 3 s; echo time (TE) = 30 ms; 21×6 mm thick axial slices; 360 volumes (the first four were “dummy” scans), flip angle = 90° , field of view (FOV) = 192×256 mm, matrix = 64×64 , voxel size = $3 \times 4 \times 6$ mm]. In addition, a T1-weighted high-resolution structural scan (64 slices \times 3 mm) was taken for anatomical overlay of activation. fMRI data were collected throughout and for 17 min after the prick test.

STATISTICAL ANALYSIS. Analysis of imaging data was performed in a multi-stage process using FEAT [functional MRI (fMRI) expert analysis tool], part of FSL [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB, Oxford, UK) Software Library; www.fmrib.ox.ac.uk/fsl]. The following prestatistic processing was applied: motion correction using MCFLIRT (motion correction using FMRIB's linear image registration tool) (Jenkinson and Smith 2001); nonbrain removal using BET (Smith 2002); spatial smoothing using a Gaussian kernel of 5-mm full-width at half-maximum (HWHM); mean-based intensity normalization of all volumes by the same factor; Gaussian low-pass temporal filtering HWHM 2.8 s. High-pass filtering could not be applied to the datasets, as this would remove important temporal information from the itch intensity model.

Statistical analysis at the first, individual subject level was carried out using a general linear modeling (GLM) approach (Friston et al. 1995). A model of itch perception was constructed from each individual's itch intensity ratings obtained in the scanner, which were linearly interpolated in MATLAB to obtain the same number of time sampling points as there were in the fMRI data. That is, because VAS ratings were obtained once every 30 s, values for scans where no rating was made were computed corresponding to values along a straight line between one VAS rating and the next using a linear interpolation in MATLAB. Each individual's model was used as a regressor for the general linear model, to find out which brain areas showed activation correlating with the changes in itch intensity rating over time. Two further regressors were defined to model the duration of the prick tests (3 s) and the duration of the prick test rating (6 s every 30 s). These regressors were included to reduce activity caused by application of the prick test and motor activity during the VAS ratings, thereby increasing statistical sensitivity for the itch-specific activation maps. Each regressor was convolved with a generalized gamma variate hemodynamic response function (mean lag: 6 s and HWHM: 6 s). The itch perception regressor was made orthogonal with respect to the prick-test regressor to ensure itch-related activation maps were not affected by the lancet skin pricks, which could cause very minor pain sensation. The estimated motion parameters for each

subject were included as covariates of no interest to reduce spurious activations due to head motion and scanner drift, thereby increasing statistical sensitivity. Only voxels for which there was signal in all subjects were included in the statistical maps.

A single contrast, itch perception versus baseline was formed. Registration to high resolution and/or standard images was carried out using FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002). Higher-level (group) statistical analysis was carried out using FMRIB's local analysis of mixed effects (FLAME) (Beckmann et al. 2003; Woolrich et al. 2004). Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 2.0$ and a (corrected) cluster significance threshold of $P = 0.01$ ($P = 0.05$ for small volume corrections) (Worsley et al. 1992). For the group analysis, registration was carried out onto the Montreal Neurological Institute (MNI) standard brain. Contrasts were formed for the atopic and the nonatopic groups but not for between-group comparison. Using pre-threshold masking (small volume correction), additional analysis restricted the region of FLAME analysis to predefined anatomical structures: the posterior insula and the middle/anterior insula bilaterally and the contralateral medial BA6 [supplementary motor cortex (SMA) and pre-SMA].

RESULTS

Laser Doppler results

All subjects reported experiencing itch when challenged with allergen and/or histamine solutions. Time course, mean intensity value, and delay between prick test and onset of changes are depicted in Fig. 1, A–C. Blood flow increased significantly more in response to type 1 allergens than to histamine ($P < 0.005$, see Fig. 1A). As shown in Fig. 1B, allergen-induced itch intensity ratings were higher (mean: 6.6 ± 1.7) than those elicited by histamine (atopic group mean: 4.2 ± 2.2 , nonatopic group mean: 2.9 ± 1.6 , $P < 0.005$). Itch sensation and increases in blood flow lasted significantly

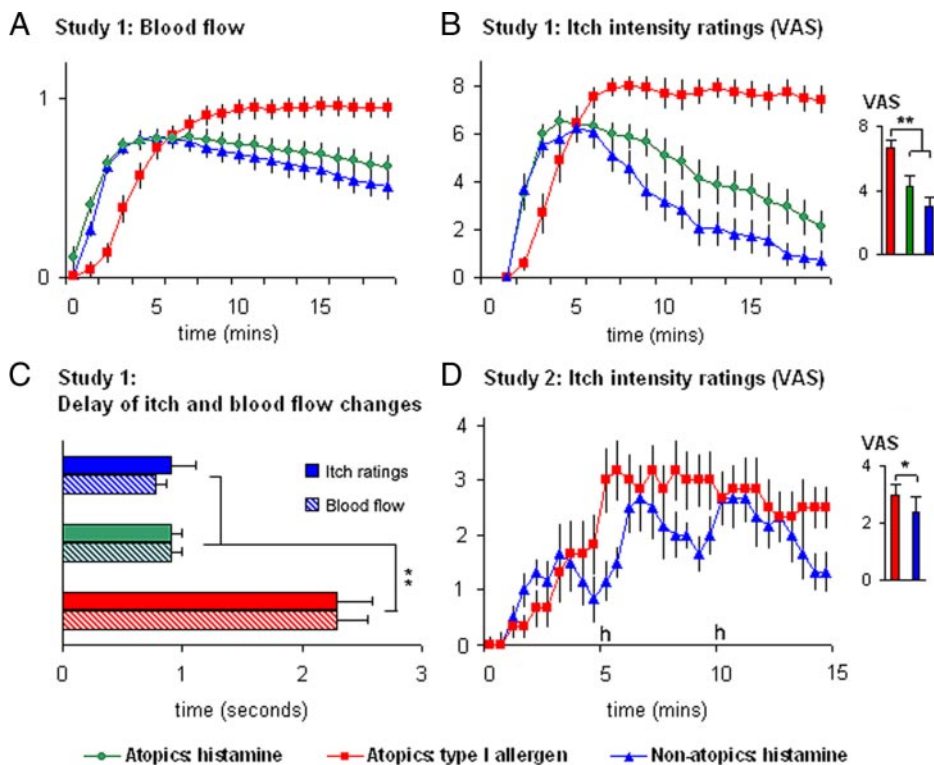


FIG. 1. *A*: mean blood flow changes (\pm SE) over time as measured by the laser Doppler. *B*: mean itch intensity ratings (\pm SE) over the duration of the experiment [visual analog scale (VAS) scale 0–10]. *C*: mean time (\pm SE) between the prick test and the initiation of itch VAS ratings and blood flow. *D*: overview of the mean itch VAS scores (\pm SE) recorded in the fMRI experiment, with mean intensity values (\pm SE) on the side (VAS scale 0–5). The letter 'h' shows the timing of the repeated histamine prick tests. **, significant difference between allergen and histamine conditions at the 0.005 level; *, at the 0.05 level.

longer in response to allergen than to histamine ($P < 0.005$, Fig. 1, A and B). Onset of itch perception coincided with onset of blood flow changes in every condition (Fig. 1C). However, increases of perceived itch intensity and blood flow increases in response to allergen occurred significantly later (>2 min) than in response to histamine (<1 min; $P < 0.001$). Histamine-induced itch intensity peaked at 2–5 min and subsequently decreased toward baseline, whereas allergen-evoked itch intensity peaked later (4–7 min) but remained stable throughout the experiment (Fig. 1, A and B). Despite the steeper decrease of itch intensity compared with blood flow changes after the first 5 min in the histamine condition, mean itch intensity ratings and blood flow changes were correlated throughout the 20-min experiment for all conditions ($P < 0.01$). There were no significant differences between groups in the histamine condition. The negative control solution (saline) did not produce a significant rise in blood flow nor any sensation of itch in any condition (data not shown).

fMRI imaging results

BEHAVIORAL. All subjects except one reported experiencing itch during the scan. The subject who did not report any itch sensation was excluded from further analysis. The average itch intensity during the scan was 3.0 ± 0.4 for allergen-induced itch, and 2.4 ± 0.6 for itch elicited by histamine. Because the histamine prick test was repeated three times while the allergen was only applied once, itch intensity ratings over time were more similar across groups than in study 1. However, as expected based on the results from the first experiment, the atopic group still experienced significantly more itch throughout the scan (1-tailed t -test, $P = 0.03$). The range of itch intensity ratings throughout the scan was ≥ 4 points on the VAS scale for each subject (mean minimum and maximum ratings were 0 and 4.14 for allergen-induced itch and 0 and 3.75 for histamine-induced itch, respectively). Between-subject variability of mean itch intensity during the scan never exceeded 1.5 points on the VAS scale. This narrow range did not permit region of interest analysis to correlate between-subject differences in itch intensity ratings with BOLD activation.

Consistent with the results from the laser Doppler study, itch ratings in response to allergens increased more slowly than itch perception in response to histamine, and remained stable at a high level after the peak (Fig. 1). The mean itch ratings for allergen-induced itch, although obtained every 30 s in the scanner, were significantly correlated with the corresponding mean ratings obtained continuously in the same condition during the laser Doppler (Spearman's ρ , $P < 0.001$). Similarly, we found a significant correlation between mean itch ratings for histamine-induced itch in the two studies during the first 5 min before the second histamine application in the fMRI study (Spearman's ρ , $P = 0.006$). These similarities were observed despite the different sites of itch induction in the two experiments (volar forearm during the laser Doppler measurements, and in between toes during the scan), the different scales used (0–10 vs. 0–5), and the differences between study populations (all female in the laser Doppler study, mixed groups in the fMRI study). The double application of the skin-prick test over each drop of allergen or histamine solution

may have contributed to our success in eliciting a robust itch sensation in the scanner environment.

Correlation between allergen-induced itch and BOLD response

Significant activation that correlated with individual allergen-induced itch ratings was found in a number of cortical and subcortical regions (Table 1). In the prefrontal cortex, significant activation was found in the subgenual and perigenual ACC and in the bilateral medial, left middle, and left lateral orbitofrontal cortex (OFC). A correlation between itch perception and BOLD response was identified in several motor areas contralateral to the site of stimulation: the left primary sensory cortex (S1), left primary motor cortex (M1), SMA, and premotor cortex (PMC). Activation in the posterior parietal cortex (PPC) was also found to correlate with reported itch perception. Subcortical areas identified in this analysis included the ventral striatum bilaterally, extending into the dorsal aspect of

TABLE 1. Areas of significant activation in response to allergen- and histamine-induced itch

	BA		x	y	z	Z Score
Allergen-induced itch						
Subgenual ACC	25	R	2	28	-6	4.53
	25	R	6	30	-10	3.1
	25	L	-10	32	-10	2.73
Subgenual ACC	32	R	12	44	-8	5.12
Perigenual ACC	24	L	-2	36	2	5.86
Medial OFC	11/12	R	10	46	-18	6.37
	11	R	2	32	-24	4.86
	12	R	2	44	-22	4.47
	12	L	-20	48	-18	3.59
Middle OFC	14/11	L	-22	28	-26	3.33
Lateral OFC	11	L	-40	30	-24	5.13
Mediodorsal thalamus (MD)	—	L	-8	-16	12	2.68
Anterior thalamus	—	L	-6	-4	8	6.07
Anterior thalamus	—	R	8	0	6	6.01
Caudate	—	L	-14	16	2	2.9
Caudate	—	R	6	14	0	3.93
Premotor cortex	6	L	-28	-6	68	2.91
SMA	6	L	-6	8	66	4.05*
	6	L	-12	18	62	3.26*
SI/postcentral sulcus	1-3	L	-46	-26	54	4.31
M1/precentral sulcus	4	L	-24	-18	74	5.76
SM1/central sulcus	3/4	L	-44	-22	62	5.76
Posterior parietal cortex	39	L	-40	-82	32	5.16
	39	L	-38	-82	28	4.8
	40	L	-50	-48	56	4.66
	40/7a	L	-34	-60	66	4.4
Histamine-induced itch						
Perigenual ACC	24	R	8	38	6	4.51
	24	L	-4	30	8	2.69
Caudate	—	R	6	8	2	5.28
	—	L	-4	12	2	4.5
Ventral caudate	—	R	10	12	-4	3.81
Ventral putamen	—	R	20	10	-4	3.03
Anterior thalamus	—	R	6	4	2	5.58
	—	R	8	0	2	2.76
	—	L	-4	-2	2	3.66
Anterior insula	—	L	-34	14	0	2.82*
	—	R	38	10	-4	2.99*
Posterior insula	—	L	-36	-22	12	3.81*

ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; SMA, Supplementary motor area; SMI, primary sensory and motor areas. *, Small volume correction.

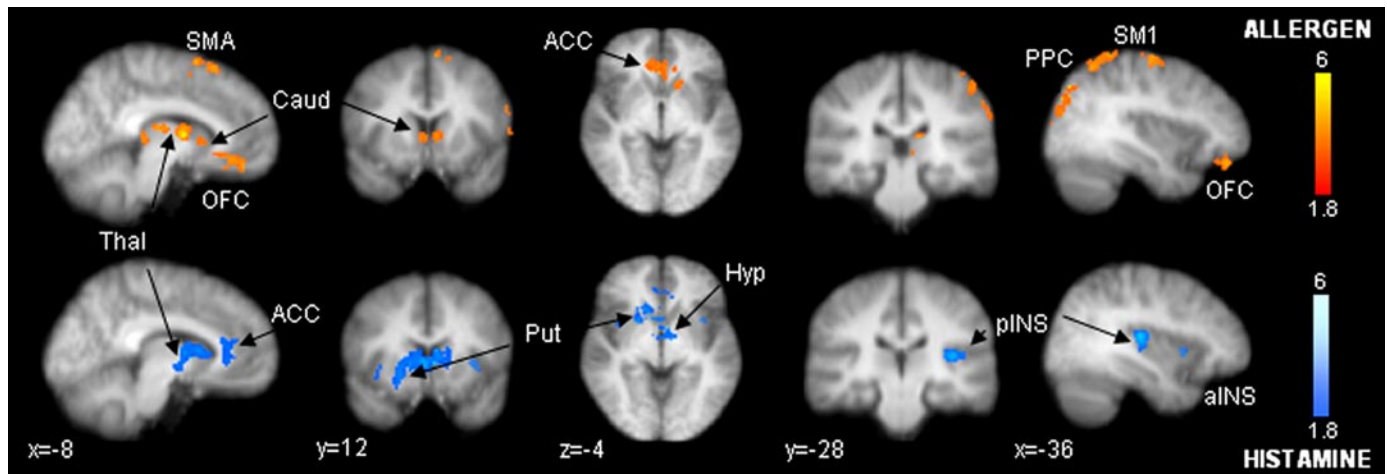


FIG. 2. The correlation of the blood-oxygen-level-dependent (BOLD) response with individual itch intensity VAS ratings at the group level yielded significant activation for allergen (red/yellow)- and histamine-induced (blue) itch. Both types of itch activated areas of the thalamus, anterior cingulate cortex (ACC), and the striatum. In addition, activation in primary and supplementary motor areas, in the posterior parietal cortex (PPC) and in the orbitofrontal cortex (OFC) correlated with itch in atopic subjects. Significant activation of the insular cortex and the hypothalamus correlated with histamine-induced itch. Images are shown according to radiological convention where R = L. SMA, supplementary motor area; Caud, caudate; OFC, orbitofrontal cortex; Thal, thalamus; ACC, anterior cingulate cortex; Put = putamen; pINS, posterior insula; aINS, anterior insula; PPC, posterior parietal cortex; SM1, primary sensory and motor areas.

the caudate nucleus head, the bilateral anterior thalamus and the left mediodorsal nucleus of the thalamus (see Fig. 3).

Correlation between histamine-induced itch and BOLD response

The histamine group showed itch-related activity in the perigenual ACC (more dorsal than the main locus of ACC activation in the atopic group) but not in the orbitofrontal cortex. Unlike the allergen group, no correlation was found between histamine-induced itch and motor areas. However, histamine-evoked itch was correlated with activity in the contralateral (left) posterior insular cortex and the anterior insula bilaterally. Subcortical areas which correlated with itch intensity ratings included the ventral striatum bilaterally, the caudate head bilaterally, the right ventral putamen, and the anterior thalamus bilaterally. (Figs. 2 and 4).

Allergen- and histamine-induced itch activation overlap

Both types of itch were correlated with activation in the ventral striatum including the head of the caudate nucleus and the anterior thalamus and in the perigenual ACC, all bilaterally (see Fig. 4). In addition, exploratory analysis indicated that despite the lack of a significant activation in the insula in

response to allergen-induced itch, levels of activity in this region were comparable across groups, with a trend toward positive correlation between itch intensity and activity in the insula bilaterally for both types of itch ($r^2 \leq 0.16$, $P \geq 0.1$). Further, visual inspection of the group activation maps at lower thresholds revealed a nonsignificant correlation between itch and the dorsal ACC for both types of itch.

DISCUSSION

Most, if not all, definitions of itch highlight the intrinsic association between itch sensation and motivation to scratch (Rees and Laidlan 1999). Although this is not accurate for every type of itch (e.g., urticaria), it nevertheless emphasizes both the motivational and the interruptive, attention-grabbing qualities of itch sensation, which may be analogous to those previously described for pain (Carroll et al. 2005; Eccleston and Crombez 1999). Chronic itch sufferers, although aware that scratching is likely to harm their skin and prolong or increase their itch sensation, still scratch). Interestingly, Yosipovitch and colleagues recently showed that scratching reduced not only itch sensation but also the histamine-induced blood flow changes (Yosipovitch et al. 2005).

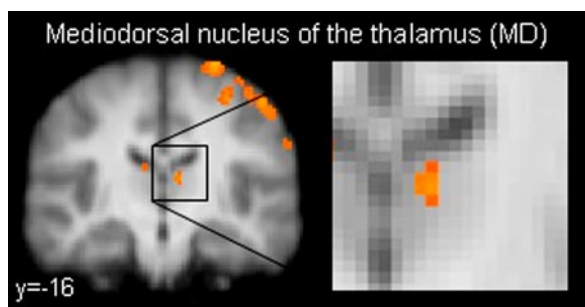


FIG. 3. The group analysis showed that itch correlated with activation of the mediodorsal nucleus of the thalamus on the left side (peak at -8 , -16 , 12). Images are shown according to radiological convention where R = L.

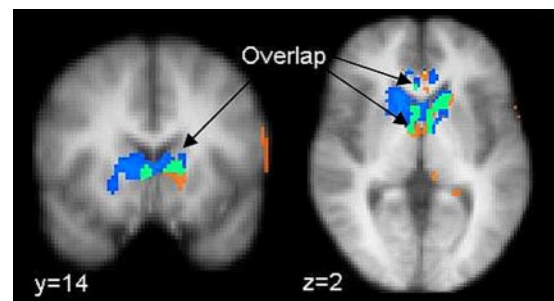


FIG. 4. At the group level, both allergen- and histamine-induced itch correlated with BOLD activity in the ventral and dorsal head of the caudate nucleus (green = overlap, yellow/red = atopics and blue = nonatopics). The activation extended into the ventral striatum for both groups: left NAcc for atopics and right NAcc and ventral putamen for histamine-induced itch in nonatopics. Images are shown according to radiological convention where R = L.

Itch sensation can have a variety of causes; many people experience a transient itch-scratch cycle after a mosquito bite. Here we investigated two types of experimentally induced itch, elicited by specific type I allergens or histamine prick tested into the skin. After a pruritic stimulus, itch intensity, skin blood flow and central blood flow changes were measured using VAS ratings and either laser Doppler flowmetry or fMRI. We identified extensive commonalities, but also some differences between allergen- and histamine-induced itch (similarly, Tracey et al. (2000) found that pain evoked by different noxious stimuli produced similar but not identical brain activation maps.)

The existence of labeled lines for itch sensation has been debated, but recent findings (Andrew and Craig 2001; Ikoma et al. 2005; Schmelz 2001) point to itch-sensitive neurons in the skin and in the spinothalamic tract. After a prick test application, histamine directly stimulates histamine type 1 (H_1)-receptors on C-pruriceptors, resulting in a wheal and flare reaction and usually an accompanying itch sensation (Yosipovitch et al. 2003). The wheal is a response to H_1 -receptor stimulation, whereas the flare is the result of the secondary release of vasoactive substances from collateral axons. In the doses used here, both allergen and histamine successfully induced intense itch in our subjects as well as a substantial wheal and flare reaction as measured with laser Doppler flowmetry. Allergen-induced itch sensation took longer to commence after the prick test and was perceived for significantly longer than the histamine-induced itch. This result was closely paralleled by laser Doppler measurements of blood flow. The later initiation of response after the administration of allergen probably relates to the interaction between the allergen and the IgE-bearing dermal mast cells. The subsequent degranulation of mast cells is known to lead to the release of a number of pharmacological agents capable of inducing itch, including histamine, platelet-activating factor, prostaglandins and proteases (Greaves 1998).

In the fMRI experiment, we attempted to diminish differences in intensity and duration between the types of itch by exploiting the additive effects of repeated histamine applications. Despite this, allergen-induced itch was rated significantly higher than histamine-induced itch. This intensity discrepancy may explain some of the differences in the itch-related activation maps for the two groups. The main finding was the significant correlation of one or both types of itch with the BOLD response in a number of areas implicated in motivational processing, e.g., food and drug cravings and compulsive behavior (Lubman et al. 2004; Mataix-Cols et al. 2004; Nakao et al. 2005; Pelchat et al. 2004; Volkow and Fowler 2000; Volkow et al. 2005; Whiteside et al. 2004). Although previous positron emission tomography (PET) studies of itch have reported activation in some of these regions, notably the insula and the supragenual anterior cingulate cortex (ACC) (Drzezga et al. 2001; Hsieh et al. 1994; Mochizuki et al. 2003), and a recent fMRI study pointed to the involvement of ventral prefrontal areas (Walter et al. 2005), this is the first time that all of these regions, including orbitofrontal, striatal, and subgenual ACC, have been implicated in itch processing.

Several of the preceding regions are known to respond preferentially to immediate rewards and are less sensitive to future rewards (McClure et al. 2004). The ventral striatum appears to encode motivation for both rewarding and aversive

events (Dreher et al. 2006; Jensen et al. 2003). The medial OFC also plays a role in monitoring the affective properties of sensory stimuli (Kringelbach 2005). We suggest that the limbic and prefrontal activation reported here reflects the subjects' desire to relieve the itch by scratching. Over a prolonged time scale, this pattern of itch-related processing may be involved in establishing uncontrollable itch-scratch cycles as commonly displayed by chronic itch patients. The ventral striatum projects to the OFC via the mediodorsal nucleus of the thalamus (MD) (Ray and Price 1993). In pathological conditions involving irresistible urges such as addiction, obesity, and obsessive compulsive disorder (Aouizerate et al. 2004; Volkow and Wise 2005), the failure to regulate the motivational drive has been linked to a dysfunction of the striato-thalamo-orbitofrontal circuit (Lubman et al. 2004; Volkow and Fowler 2000). Here, the striatum, thalamus and OFC were found to be significantly correlated with itch intensity. BOLD signal in the ventral and dorsal striatum was significantly correlated with both types of itch. Although the ventral striatum has been associated specifically with craving (Heinz et al. 2004), activation more dorsally in the caudate head may mediate motivated or goal-directed behaviors (Delgado et al. 2004). That the MD and the OFC were significantly activated only in the allergen condition could be due to the higher itch intensity reported in this condition. Note that no direct between-group contrast was performed, and we did not obtain dose-response curves for our pruritic stimuli.

Typical definitions of itch highlight the high dependency between itch and motivation to scratch. This co-morbidity has informed the interpretation of the frontal activations reported here. The left lateral OFC has been implicated in response suppression, especially to previously rewarded actions (Arana et al. 2003; Elliott et al. 2000). The correlation to itch intensity found in the supplementary and premotor areas as well as the ACC also points to active suppression of scratching or other movement during the scan (Rushworth et al. 2004; Watanabe et al. 2002). Motor areas were activated in response to itch in previous studies of histamine-induced itch (Drzezga et al. 2001; Hsieh et al. 1994; Mochizuki et al. 2003). Further, activation of the ACC and the posterior parietal cortex has been consistently reported in functional imaging studies of both itch and attention (Botvinick et al. 2004; Drzezga et al. 2001; Hsieh et al. 1994; Mochizuki et al. 2003). The main sites of cingulate activation identified in previous studies of itch were more dorsal than the ACC activation reported here, which may reflect the different imaging modalities (PET/fMRI) and their spatial resolution and important differences in data analysis. Here, itch intensity ratings collected throughout the experiment were correlated with the fMRI data and should thus reflect temporal changes in the itch sensation. In contrast, previous itch PET studies used either subtraction analysis (histamine-saline) or correlated histamine concentration/peak unpleasantness ratings with the imaging data (Drzezga et al. 2001). Interestingly, it has been suggested that processing in the pregenual ACC might be associated with C-fiber activation and the "suffering" component of pain, whereas more dorsal cingulate areas are thought to be engaged in premotor planning and might have little involvement in sensation (Vogt 2005). The parietal cortex also serves a crucial role in transforming sensory input into motor output (Behrmann et al. 2004). A study of attention and pain, another unpleasant sensation,

showed modulation of stimulus-related activity in both the subgenual ACC and the medial OFC (Bantick et al. 2002).

Itch sensation is mediated from the periphery by small-diameter primary afferents, which project to the insula via the dorsal horn and the thalamus (Andrew and Craig 2001; Jinks and Carstens 2000). The insula is important in the processing of pain (e.g., Brooks et al. 2002; Coghill et al. 1994) and has been activated in response to an array of emotional and interoceptive stimuli, e.g., as a neural substrate of food cravings (Pelchat et al. 2004). Here we found activation of the contralateral (left) posterior insula and the bilateral anterior insula in response to histamine-induced itch, and primary sensory cortex (SI) in response to atopic itch. The insula and SI were activated in response to itch in a previous study of itch which employed histamine concentrations of $\leq 8\%$ (Drzezga et al. 2001) but not in two studies where lower concentrations ($< 0.01\%$) were used (Hsieh et al. 1994; Mochizuki et al. 2003). Together with our results, this suggests that the involvement of the insula and SI in itch processing varies with stimulus type and intensity.

The significant correlations between itch intensity ratings and laser Doppler flowmetry measurements observed here point to a high itch-rating accuracy in our experimental conditions. Although itch intensity ratings obtained in the first study were continuous, VAS ratings were only obtained every 30 s in the fMRI study and subsequently interpolated to provide a value for each functional scan. However, the validity of this method is supported by the close correlation between the itch ratings obtained in the two studies despite their different study populations. Another constraint of the imaging study was the unfeasibility of using high-pass filtering as this would remove important temporal information from the model. Explicit modeling of motion parameters was employed to remove slow motion or scanner drift noise from the data.

In conclusion, we have demonstrated extensive involvement of the brain motivation circuitry in response to two types of experimental itch. The contribution of striatal and limbic regions reflecting the desire to scratch highlights the deep entanglement of perception with motivation/action. It is this entanglement that underpins the harm caused by uncontrollable itch-scratch cycles in chronic itch.

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