Published in final edited form as:
Br J Dermatol. 2009 November ; 161(5): 1072–1080. doi:10.1111/j.1365-2133.2009.09308.x.

Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis

Y. Ishiuji[*,†], **R.C. Coghill**[‡], **T.S. Patel**[*], **Y. Oshiro**[‡], **R.A. Kraft**[§], and **G. Yosipovitch**[*,‡]

[*]Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, U.S.A.

[‡]Department of Neurobiology & Anatomy & Neuroscience Center, Wake Forest University School of Medicine, Winston-Salem, NC 27157, U.S.A.

[§]Department of Biomedical Engineering, Wake Forest University School of Medicine, Winston-Salem, NC 27157, U.S.A.

[†]Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan

Summary

Background—Little is known about brain mechanisms supporting the experience of chronic puritus in disease states.

Objectives—To examine the difference in brain processing of histamine-induced itch in patients with active atopic dermatitis (AD) vs. healthy controls with the emerging technique of functional magnetic resonance imaging (fMRI) using arterial spin labelling (ASL).

Methods—Itch was induced with histamine iontophoresis in eight patients with AD and seven healthy subjects.

Results—We found significant differences in brain processing of histamine-induced itch between patients with AD and healthy subjects. Patients with AD exhibited bilateral activation of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), retrosplenial cingulate cortex and dorsolateral prefrontal cortex (DLPFC) as well as contralateral activation of the caudate nucleus and putamen. In contrast, healthy subjects activated the primary motor cortex, primary somatosensory cortex and superior parietal lobe. The PCC and precuneus exhibited significantly greater activity in patients vs. healthy subjects. A significant correlation between percentage changes of brain activation was noted in the activation of the ACC and contralateral insula and histamine-induced itch intensity as well as disease severity in patients with AD. In addition, an association was noted between DLPFC activity and disease severity.

Conclusions—Our results demonstrate that ASL fMRI is a promising technique to assess brain activity in chronic itch. Brain activity of acute itch in AD seems to differ from that in healthy subjects. Moreover, the activity in cortical areas involved in affect and emotion correlated to measures of disease severity.

Correspondence Gil Yosipovitch. gyosipov@wfubmc.edu.

Conflicts of interest
None declared.

Keywords

anterior cingulate cortex; arterial spin labelling; atopic dermatitis; functional magnetic resonance imaging; histamine; pruritus

Pruritus is a most distressing symptom in many dermatological and systemic disorders – the most notable being atopic dermatitis (AD).1 In its chronic form, pruritus profoundly impacts quality of life and constitutes an enormous burden to society. Pruritus is so central to AD that it may frequently be referred to as 'the itch that rashes'.2 Currently, the understanding of the pathophysiology of pruritus is poor. Present data points towards an intricate interplay between peripheral and central mechanisms.3

Neuroimaging studies until recently were focused on brain imaging of histamine-induced itch in healthy human subjects. In healthy humans, acute histamine-induced itch coactivates the anterior cingulate cortex (ACC), the insular and primary somatosensory cortices, premotor and supplementary motor areas, cerebellum and thalamus.4–13 A recent study using positron emission tomography (PET) was the first to image brain processing of itch in patients with AD in remission and demonstrated similar areas of activation to those of healthy subjects, with higher activation in patients with AD in the contralateral thalamus, ipsilateral putamen and pallidum.14 However, as yet there is no study that has examined brain activation of itch in patients with active chronic itch.

The neuroimaging of pruritus-related brain activity is a methodogical challenge. To date, studies have used PET and functional magnetic resonance imaging (fMRI) employing blood oxygen level dependent (BOLD) contrast.4,5,7,9,10,12 Although PET is fully quantifiable, radiation exposure and methodological complexities associated with this neuroimaging technique limit its routine use. In addition, the BOLD technique is suited to a biphasic stimulus model where sensory stimuli are turned on and off within a few seconds. However, the biphasic stimulus model is not suitable for experimentally induced itch, which usually takes a few minutes to reach peak intensity. Recent studies have been performed to overcome this limitation by manipulating the time course of itch with repeated itch induction with intermittent cooling or local anaesthetics.6,11 These experimental designs are rather complex to perform. The emerging technique of fMRI using arterial spin labelling (ASL) appears more suited to assess pruritus-related brain activity than the widely adopted BOLD method. Reasons include improved sensitivity for slow changes in neural activity (> 30 s) and better comparisons between different subject groups.15,16

In the present study we evaluated the central processing of histamine-induced pruritus in patients with AD with active disease and healthy subjects using the emerging technique of ASL fMRI. We show that the neural networks activated by pruritus differ in these two groups.

Patients and methods

Subjects

A total of 15 subjects participated in this study: eight patients with AD (five men, three women; mean ± SD age 33.1 ± 10.8 years) and seven healthy volunteers (three men, four women; mean ± SD age 34.6 ± 10.0 years). All subjects were right handed. AD was diagnosed by the criteria of Hanifin and Rajka.17 The Eczema Area and Severity Index (EASI) score of the patients with AD, which was developed to provide a reliable and sensitive tool for easy assessment of the severity of AD across a wide range of patients, was in the range of 8.4 to 54.3 and included two patients with mild, three with moderate and

three with severe AD (mean ± SD EASI score 24.9 ± 16.4).18,19 Healthy volunteers were matched for age and gender. All procedures were approved by the Institutional Review Board of Wake Forest University School of Medicine. All subjects provided written informed consent and were free to withdraw from the experiment at any time.

Induction of itch sensation

Itch was evoked by iontophoresis of histamine into lesional skin of the ventral forearm skin in patients with AD as well as into skin at the ventral forearm of the dominant (right) hand of healthy controls using a round iontophoresis electrode 14 mm in diameter. Although endogenous histamine has no significant role in itch of AD,20 histamine was chosen as the itch stimulus as it is the most familiar pruritogen and is still frequently used in both human and animal experimental itch models. In addition, histamine has been shown to intensify itch in the lesional skin of AD.21,22

For iontophoresis, a 1% solution of histamine was dissolved in 2% methylcellulose gel (Sigma, St Louis, MO, U.S.A.) and was administered with a current of 200 μA for 30 s (PF3826 Perilont Power device; Perimed, Stockholm, Sweden). Iontophoresis was terminated 30 s prior to start of image aquisition. Histamine iontophoresis was performed twice during the experimental session, with an interval of 20 min between trials.

Psychophysical measurements

Subjects used a 100-mm visual analogue scale (VAS) to report perceived intensity of itch in the presence and absence of histamine stimuli ranging from 0 (no sensation) to 100 mm (most intense sensation imaginable) at the end of each fMRI series. Of note, the VAS scale functions as a true ratio scale23 and is sensitive to small changes in magnitude of perceived itch intensity.22,24 Patients were asked to rate their baseline itch immediately prior to the scanning experiment.

Imaging acquisition

All images were acquired on a 1.5 Tesla MRI scanner (GE Healthcare, Milwaukee, WI, U.S.A.) using a four-channel neurovascular MR coil array (Medrad, Inc., Warrendale, PA, U.S.A.). Total imaging protocol consists of localizer images acquired for graphical prescription, a high-resolution anatomical T1-weighted image, and four fMRI experiments (two rests and two histamine-induced itch).

Anatomical image acquisition

High-resolution T1-weighted anatomical images were used to identify regions of activation, to classify tissues, to normalize images to a standard space, and to screen for abnormalities. T1-weighted structural scans were obtained using an inversion prepared 3D spoiled gradient echo sequence using a matrix size of 256 × 256, field of view (FOV) of 24 cm, echo time (TE) of 1.9 ms, and inversion preparation time of 600 ms, flip angle of 20°, slice thickness of 1.5 mm with no gap between slices, and 128 slices, giving an in-plane resolution of 0.94 mm.

T1 map image acquisition

Accurate quantitative cerebral blood flow (CBF) maps require that the T1 of the tissue be measured at each voxel. T1 maps were calculated from data acquired from a separate inversion recovery (IR) echo-planar imaging (EPI) sequence. A global inversion C-shaped frequency offset corrected inversion (C-FOCI) pulse is used to minimize underestimating the T1 due to fresh spins perfusing into the imaging slice. Twelve inversion times (TIs) were acquired logarithmically from 10 ms to 6 s with a repetition time (TR) of 10 s. After a

deliberate 6-s delay, the first volume was acquired without an inversion pulse to obtain an M0 image. Thirteen imaging volumes were then acquired in a total scan time of 2 min 10 s. All other imaging acquisition parameters (FOV, matrix size, TE, flip angle, slice thickness, slice location etc.) are identical to the Q2TIPS-FAIR protocol as described in the next section. The T1 for each voxel was calculated by curve fitting the IR curve to a three-parameter decaying exponential model.25

Perfusion image acquisition

CBF was measured with quantitative imaging of perfusion using a single subtraction with thin slice TI_1 periodic saturation (QUIPSS II TIPS, also known as Q2TIPS)26 with flow-sensitive alternating inversion recovery (FAIR).27 The Q2TIPS-FAIR sequence is a multislice sequence that incorporates saturation pulses to minimize the uncertainty associated with tagged blood's transit time into the imaging slice.28 The saturation pulses in implementation of Q2TIPS are very selective suppression (VSS) radio frequency pulses,29 which are applied every 25 ms between 800 ms (TI_1) and 1200 ms (TI_{1s}). The VSS pulses saturate a 2-cm slab of tissue with a 1-cm gap between the saturation slab and the first imaging slice. Our current implementation of the Q2TIPS-FAIR sequence uses a C-FOCI pulse ($\beta = 1361$, $\mu = 6$).30 A C-FOCI pulse is used instead of the standard adiabatic hyperbolic secant pulse to improve perfusion sensitivity by minimizing slice imperfections.31,32 The 11 oblique slices were prescribed parallel to the anterior commissure/posterior commissure line and were acquired sequentially, inferior to superior. This provided coverage from the vertex to the ventral aspect of the thalamus and prefrontal cortex. Other imaging parameters were as follows: TE 28 ms, TI_1 800 ms, TI_{1s} 1200 ms, TI 2000 ms, TR 3000 ms, receiver bandwidth 62.5 kHz, flip angle 90°, FOV 24 cm (frequency) × 18 cm (phase), acquisition matrix 64 × 48 (11 slices, 8 mm thickness, 0 mm slice gap), and frequency encoding direction anterior/posterior. A diffusion gradient with an equivalent *b* value of 5.25 $mm^2\ s^{-1}$ is added to suppress intra-arterial spins.33

The Q2TIPS-FAIR sequence was used to acquire 60 label/control pairs (slice selective inversion/global inversion) in 6 min 30 s. These label/control pairs are pair-wise subtracted and then averaged to generate a perfusion-weighted image. The first 30 s (five label/control pairs) is used to establish steady state. During this 30 s a single-shot EPI proton density (M0) image is acquired. This M0 image serves as an internal reference to scale the perfusion-weighted images appropriately to calculate absolute quantitative CBF maps according to the general kinetic model described by Buxton *et al.*34

Statistical analysis of regional signal changes within the brain

The functional image analysis package FSL [Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (Center for FMRIB, University of Oxford, Oxford, U.K.)] was used for image processing and statistical analysis. The CBF data were movement corrected and spatially smoothed using a 10 mm 3D isotropic Gaussian kernel. Each CBF image was scaled by its mean global intensity (intensity normalization) to minimize variability due to global CBF changes. Next, each subject's CBF images were registered to their structural data using a seven-parameter linear 3D transformation and transformed into standard stereotaxic space (as defined by the Montreal Neurological Institute) using a 12-parameter linear 3D transformation.35,36 Standard general linear model-based analyses were performed separately to identify effects due to histamine administration and disease status, with fixed-effects models within subjects and random effects models between subjects.37 Clusters of voxels exceeding a Z score > 2.3 and $P < 0.05$ were considered statistically significant.38

Statistical analysis of psychophysical data between itch intensity, disease severity and specific brain region

Better to delineate the relationship between brain activity, perceived itch intensity and EASI score, percentage CBF changes were extracted from the ASL data activated brain regions such as the ACC, posterior cingulate cortex (PCC), retrosplenial cingulate cortex (RSC) and dorsolateral prefrontal cortex (DLPFC) bilaterally, and the contralateral insula and caudate nucleus.39

Spearman's correlation tests were performed to examine the correlation between the percentage change of CBF of each activated brain region, EASI score and the intensity ratings of itch (JMP software; SAS Institute, Cary, NC, U.S.A.). Data are presented as mean ± SD; $P < 0.05$ is considered statistically significant.

The difference in global cerebral blood flow between atopic dermatitis and healthy subjects

Intergroup differences in global CBF can complicate interpretation of regional brain activation. To determine if such differences occurred between patients with AD and healthy subjects, we calculated global grey matter CBF for each CBF image and evaluated differences using a single factor between-subjects analysis of variance.

Results

Itch intensity

At the beginning of the imaging session patients with AD had a significantly higher mean ± SD baseline itch intensity (16 ± 19) (VAS) than healthy controls (0 ± 0, $P < 0.0001$). Histamine-induced itch intensities were significantly higher than baseline itch intensity in both patients (16 ± 19 vs. 64 ± 20, $P < 0.0001$) and healthy controls (0 ± 0 vs. 35 ± 13, $P < 0.0001$). A significant difference was noted in mean ± SD histamine-induced itch intensity between AD and healthy controls (64 ± 20 vs. 35 ± 13, $P < 0.0001$).

Grey matter cerebral blood flow

Blood flow in the grey matter did not differ significantly between patients with AD (65.95 ± 4.55) and healthy control subjects (64.49 ± 3.38) ($F = 0.06$, $P < 0.8$). However, substantial within-group variation between individuals was observed, so subsequent regional analyses were conducted using intensity normalization.

Significant differences in brain processing of itch between atopic dermatitis and healthy subjects after histamine stimulation

After histamine stimulation, brain activation in the patients with AD was significantly greater than baseline within bilateral portions of the ACC, PCC and RSC as well as the DLPFC. This was also true for the contralateral caudate nucleus and putamen as well as the anterior and posterior insular cortices (Fig. 1 and Table 1). Of note, histamine stimuli did not activate the primary somatosensory cortex (S1), motor area or the thalamus to a detectable level. In healthy subjects, after histamine stimulation, brain activation was significantly greater than baseline contralaterally within the primary motor cortex, S1 and superior parietal lobe (Fig. 1 and Table 2). However, there was no activation within the DLPFC, ACC or basal ganglia. When histamine-induced itch-related activation (itch vs. baseline) was compared between patients and normals, the PCC and precuneus exhibited significant differences between groups. These brain regions were more active in patients vs. healthy subjects (Fig. 2 and Table 3). Patients activated these areas while normals deactivated these

areas. Of note, there were no significant differences in brain activity during the rest condition between the patients and healthy subjects.

Correlation between itch intensity, disease severity and brain activity in atopic dermatitis

There was a significant correlation between percentage changes of brain activation in the ACC and histamine-induced itch intensity as well as disease severity (EASI score) (r^2 = 0.26, $P < 0.05$ and $r^2 = 0.45$, $P < 0.005$, respectively). In addition, there was a significant correlation between percentage changes of brain activation in the contralateral insula and histamine-induced itch intensity ($r^2 = 0.34$, $P < 0.02$). There was also significant correlation between the percentage change of brain activation in DLPFC and disease severity ($r^2 = 0.30$, $P < 0.03$).

No correlation was observed between histamine-induced itch intensity, disease severity and brain activity in bilateral PCC.

Discussion

The present study using ASL fMRI provides new insights regarding the brain processing of experimentally induced itch in active AD, which differs from healthy skin. The ASL fMRI technique appears well suited to assess pruritus-related brain activity and offers several advantages over the previously employed PET and BOLD fMRI methods. The main advantage of ASL fMRI over BOLD fMRI is its superior functional sensitivity when the alternating period between the resting state and activation is greater than a few minutes,[40,41] such as is the case in experimentally induced pruritus. While previous fMRI studies have used BOLD contrast as a marker for neural activation, baseline drift effects result in poor sensitivity for detecting slow variations in neural activity that may be seen with pruritus. Such effects may be overcome by manipulating the time course of itch sensation with repeated itch induction, intermittent cooling or local anaesthetics, but such experimental designs are highly complex.[6,11] The ASL method was recently found to be a suitable fMRI tool to assess tonic pain and is sufficiently sensitive to measure 5–10% changes in regional CBF.[42] The authors suggest that the ASL method would be better suited for studies involving chronic pain and prolonged pain, which are difficult to assess with BOLD fMRI. These findings further support the use of this technique in imaging of chronic itch states.

Chronic itch is considered a multidimensional phenomenon, which contains sensory, affective, cognitive and emotional aspects very similar to chronic pain.[43] The significant brain activation in patients with AD in the ACC, PCC, RSC, insula and DLPFC, cortical areas which are involved in emotional processing, memory and reward behaviour, are consistent with this notion.

The somewhat surprising results of the current study are that we do not demonstrate any significant activation of the ACC and DLPFC with histamine-induced itch in healthy controls, in contrast to previous studies using PET and BOLD fMRI in healthy subjects.[4–12] Possible explanations for this discrepancy are differences in the severity of itch between studies. The lack of significant differences in brain activity in the ACC and DLPFC between the healthy subjects and patients with AD when histamine-induced itch was compared with baseline is likely to be related to subthreshold activity in healthy subjects.

A recent study by Schneider *et al.*[14] assessed brain activation in patients with AD in remission and detected significantly higher activation in patients with AD in the contralateral thalamus and in the ipsilateral basal ganglia, while healthy controls had higher activation in the ipsilateral premotor cortex and PCC. In contrast, we observed that patients

with active disease exhibited significantly greater histamine-induced itch-related activity in the PCC than healthy controls. Possible explanations for the discrepancy between our study and the previous study may reflect the use of different methodologies and patient populations. Schneider *et al.* evoked extremely intense itch with a large spatial distribution, yet did not demonstrate a psychophysical difference between patients and controls. Thus, differences in brain activation cannot be readily attributed to mechanisms directly related to the processing of perceptual aspects of itch. Moreover, none of their patients had active disease. In contrast, we induced a mild itch with a small spatial distribution in our healthy controls whereas the same stimulus in atopics with active disease provoked a profound itch that possibly reflects the known hypersensitivity of nerve fibres in atopic subjects.

Our study aims differed from previous brain imaging studies of itch in healthy subjects and patients with AD in remission, as we specifically sought to assess brain activity in an active disease state and a hypersensitive condition similar to brain imaging studies of hyperalgesia performed in neuropathic pain.44 An analysis of multiple brain imaging studies of chronic pain conditions shows that there is a reduced response to acute pain stimuli in sensory cortices such as S1, S2 and thalamus.45 The authors suggest that chronic pain may reflect decreased sensory processing and enhanced emotional and cognitive processing. Patients with chronic itch may exhibit similar diminished responsiveness in these sites.

The ACC in particular has been heavily implicated in emotional processing of sensory stimuli such as pain and itch,4,5,7,46 and activity in this area may account for the affective dimension of the itch experience. In addition, the posterior ACC (also known as the midcingulate region) has a role in the reward mechanism.47 Our previous studies documenting brain activation using BOLD fMRI in healthy volunteers did not demonstrate robust activation in this area (unpublished data) and thus led us to image the brain with the ASL technique as mentioned above.

The significant activity of the anterior and posterior insular cortex in chronic itch in AD is most probably associated with their capability to process convergent information to produce an emotionally relevant context for sensory experience such as pain, touch, sight, taste and itch.48 This is an important region for somatosensory processing and may form a corticolimbic pathway for some sensations.49

The significant activity in patients with AD in the RSC and PCC deserves special attention. Previous itch brain imaging studies in healthy subjects have not reported any activation in the RSC. This area has been shown to be a part of a network that mediates topokinetic (spatial) navigation and memory by functional imaging.50–52

The perception of itch is also highly influenced by our memories and expectations. It is well noted when we discuss the topic of itch we feel the urge to scratch. The PCC is an area of brain heavily involved with memory.53,54 Mochizuki *et al.*10 have previously shown in healthy subjects that the PCC was activated by itch. Given the relentless nature of chronic pruritus, memories as well as emotions associated with pruritus are expected to be greater in subjects with AD and thus may account for the increased activity in these brain areas when compared with healthy controls. The activation of the precuneus has not been previously reported in itch. This area has been rarely associated with chronic pain: a recent study demonstrated it to be activated in chronic pain of burning mouth syndrome.55 Recent functional imaging suggests a central role for the precuneus in a wide spectrum of highly integrated tasks, including visuospatial imagery, episodic memory retrieval and self-processing operations.56 These functions could be associated with the cognitive sequela of chronic itch.

The prefrontal cortex (PFC) is another area that was highly activated in patients with AD. The PFC has been frequently described in experiments involving attention, working memory, motivation (reward expectancy-related) and goal-directed processes.[57–59] Therefore, PFC activation may be likely to mediate part of the cognitive dimension of itch processing associated with localization and encoding of the attendant stimulus. Our results support similar findings by Leknes *et al.*[8] Furthermore, the PFC may have a role in scratching. We recently reported that repetitive scratching induced brain activity in the DLPFC, while deactivating the ACC and PCC.[60] It is thus possible that scratching is perceived as inhibiting itch, as rewardable and as pleasurable through these sites.

This is the first study that demonstrates an association between severity of a chronic itch state (as assessed by objective measures) and itch-induced brain activity (ACC, insula and DLPFC). These findings suggest that the ACC, insula and DLPFC may be excellent targets for future drugs that reduce activity in these areas, thus decreasing the augmented perception of itch in AD and other forms of chronic itch and pain.

Chronic itch has many similarities to chronic pain. Several brain-imaging studies of patients with chronic neuropathic pain suggest a difference between acute and chronic pain processing. Some studies have suggested that features of the brain processing of experimentally induced pain in chronic pain conditions are an increase in activity in the insula and ACC[61] and a lack of or reduced activity in regional CBF in the somatosensory cortices (S1 and S2).[61,62] Similar findings are noted in the current study in regard to increased activity of the ACC and insula in chronic itch. Both these areas are involved in central neural hypersensitization. However, there are notable differences such as activation of the RSC and PCC that has been rarely reported during noxious stimuli[63,64] and not reported in chronic pain.[65] These areas may play a unique role in chronic itch states.

In conclusion, this study demonstrates ASL fMRI to be sufficiently sensitive to detect regional itch-induced changes in CBF in chronic itch states and in healthy controls. By this technique, we were able to show that the brain imaging of histamine-induced itch in AD differs from that of healthy subjects. Moreover, the current study demonstrated a significant correlation between the itch intensity as well as the severity of AD and brain activation in the ACC. Future studies that assess the central processing of pruritus in other chronic pruritic conditions and techniques that can attenuate this itch response by targeting the central nervous system will be of major interest.

Acknowledgments

This study was sponsored by the NEASE (National Eczema Association for Science and Education). G.Y. is supported by NIH AR55902. R.C.C. is supported by NIH NS39426 and DA20168.

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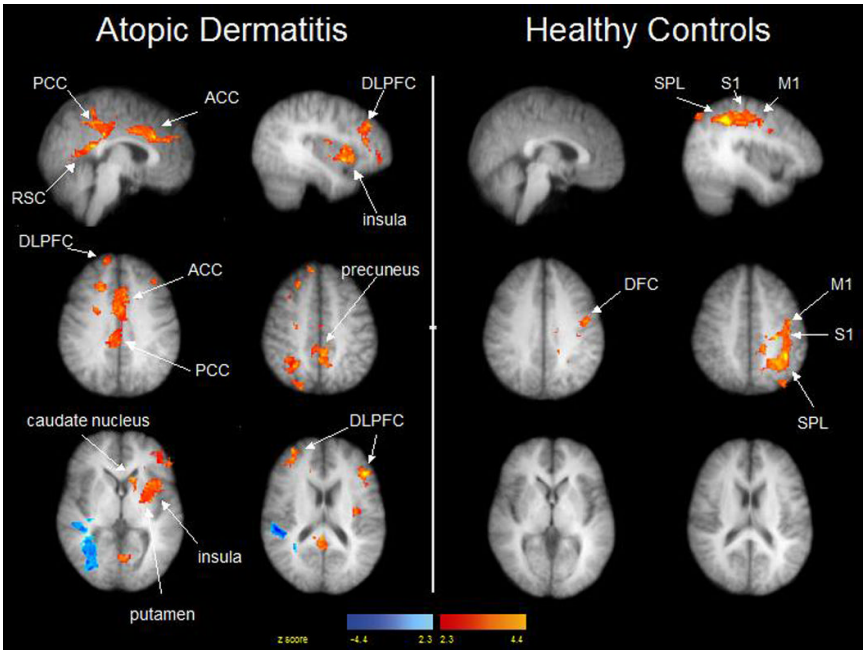

Fig 1.

Brain activation during histamine stimuli in atopic dermatitis (AD) and healthy subjects. In the healthy controls, brain activation was identified contralaterally within the primary motor cortex (M1), primary somatosensory cortex (S1) and superior parietal lobe (SPL). However, there was no activation within the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) or basal ganglia. In patients with AD, brain activation was identified bilaterally within the ACC, posterior cingulate cortex (PCC) and retrosplenial cingulate cortex (RSC) as well as the DLPFC and the contralateral caudate nucleus, putamen and anterior and posterior insular cortices. These images are located at *x*_−46, *x*_−38, *x* 34, *x* 4 mm, *y*_46, *y*_14, *y*_−8, *y*_−48 mm, *z*_2, *z*_16, *z* 36 and *z*_46 mm in standard stereotaxic space (image left corresponds to subject's right).35›36 Red is activation. DFC, dorsofrontal cortex.

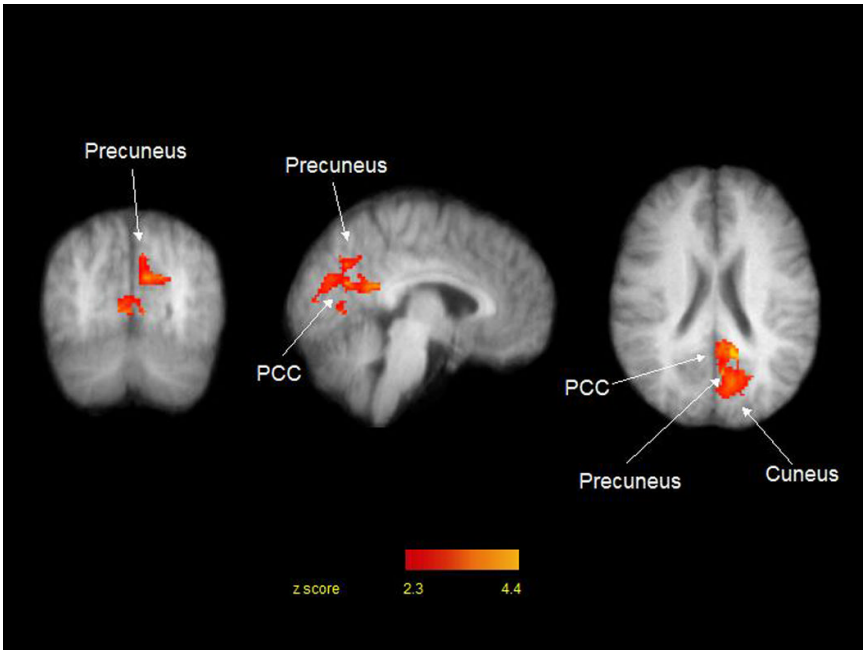

Fig 2.

The difference between patients with atopic dermatitis and healthy controls in histamine-induced brain activation was identified within the posterior cortex (PCC), precuneus and cuneus. These images are located at *x*_−4 mm, *y*_−66 mm, *z*_22 mm in standard stereotaxic space (image left corresponds to subject's right). The statistical results of activation from all subjects are shown in red and superimposed on the average structural magnetic resonance image (grey colour).

Table 1

Histamine-induced activation in atopic dermatitis

		Z score	*x*	*y*	*z*
Right	Dorsal PCC (BA31)	4.59	8	−62	10
Left	Dorsal PCC (BA31)	3.22	−2	−50	14
Right	Ventral ACC (BA24)	4.47	2	32	24
Left	Ventral ACC (BA24)	3.62	−2	24	26
Right	Middle frontal gyrus (BA8)	4.45	22	28	40
Right	Middle frontal gyrus (BA10)	4.45	36	58	16
Right	DLPFC (BA46)	3.42	42	42	18
Left	DLPFC (BA46)	4.44	−46	32	14
Right	Dorsal PCC (BA31)	4.42	10	−32	42
Right	DLPFC (BA9)	3.39	18	60	32
Left	DLPFC (BA9)	3.45	−38	34	34
Right	Insula mid?	4.29	−38	6	−6
Right	Posterior insula	3.87	−34	−6	−4
Right	Anterior insula	3.46	−32	12	4
Right	Ventral PCC (BA23)	2.93	2	−26	28
Left	Ventral PCC (BA23)	3.12	−4	−50	16
Right	Includes frontal eye field, SFG (BA8)	3.46	36	18	50
Left	Includes frontal eye field, SFG (BA8)	3.53	−36	34	38
Right	PMA (BA6)	3.17	2	−14	50
Left	PMA (BA6)	3.51	−2	−14	50
Right	Paracentral lobe (BA5)	3	2	−42	50
Left	Paracentral lobe (BA5)	3.51	−2	−42	48
Right	Precuneus (BA7)	3.59	2	−50	46
Left	Precuneus (BA7/BA5)	3.61	−2	−46	46
Right	IPL (BA7/BA40)	3.35	32	−62	44
Right	SPL (BA7)	3.58	26	−72	54
Right	Dorsal ACC (BA32/BA8)	3.64	6	18	34
Left	Dorsal ACC (BA32/BA9)	3.68	−2	32	26
Right	RSC (BA29/BA30)	4.17	8	−40	18

		Z score	*x*	*y*	*z*
Left	RSC (BA29/BA30)	3.37	−2	−44	18
Right	Frontopolar area (BA9/BA10)	3.11	32	50	20
Left	Putamen	3.73	−24	0	10
Left	IFG (BA45)	3.59	−50	36	8
Left	Caudate nucleus	3.41	−16	12	2
Right	Visual association cortex (BA18)	3.2	2	−68	2
Left	Visual association cortex (BA18)	3.19	−4	−70	2
Left	Inferior prefrontal gyrus (BA47)	2.79	−48	48	−8
Left	Anterior entorhinal cortex (BA34)	3.7	−14	−4	−12

PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; PMA, premotor area; IPL, inferior parietal lobe; SPL, superior parietal lobe; RSC, retrosplenial cingulate cortex; IFG, inferior frontal gyrus. Brodmann areas of the brain are given in parentheses. Locations (*x*, mediolateral; *y*, rostrocaudal; *z*, dorsal-ventral) are according to the Talairach coordinate system. The *Z* score represents the normalized transformation of *T* statistics values that describe the fit of the repressors with brain activation.

Table 2

Histamine-induced activation in healthy subjects

		Z score	*X*	*y*	*z*
Left	IPL (BA40)	4.38	−38	−44	42
Left	S1	4.12	−40	−24	50
Left	M1	4.09	−44	−16	38
Left	SPL	3.54	−30	−62	54
Left	Precuneus	3.33	−16	−42	48

IPL, inferior parietal lobe; S1, primary somatosensory cortex; M1, primary motor cortex; SPL, superior parietal lobe. Brodmann areas of the brain are given in parentheses. Locations (*x*, mediolateral; *y*, rostrocaudal; *z*, dorsal-ventral) are according to the Talairach coordinate system. The *Z* score represents the normalized transformation of *T* statistics values that describe the fit of the repressors with brain activation.

Table 3

The difference in histamine-induced brain activation between atopic dermatitis and healthy controls

		***Z* score**	***x***	***y***	***z***
Left	Visual association cortex (BA19)	3.99	−34	−76	34
Left	Dorsal PCC (BA31)	3.97	−10	−52	26
Left	Precuneus	3.6	−8	−72	26
Left	Cuneus	2.65	−8	−76	18

PCC, posterior cingulate cortex. Brodmann areas of the brain are given in parentheses. Locations (*x*, mediolateral; *y*, rostrocaudal; *z*, dorsal-ventral) are according to the Talairach coordinate system. The *Z* score represents the normalized transformation of *T* statistics values that describe the fit of the repressors with brain activation.