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Itch and the Brain

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Abstract

The sensation of itch – defined as unpleasant sensation inducing the urge to scratch – is processed by a network of different brain regions contributing to the encoding of sensory, emotional, attention-dependent, cognitive-evaluative and motivational patterns. Patients with atopic eczema show different activation patterns and kinetics compared to healthy volunteers. This review summarizes current studies investigating itch in the brain.

Itch is the major symptom of many diseases; yet it is still difficult to measure objectively. Recent technological advances in the field of brain imaging paved the way for neuroimaging studies on central itch pathways. Positron emission tomography (PET) Scan studies and later studies using functional magnetic resonance imaging (1.5 and 3 Tesla) technology were able to show that itch is processed by a network of brain regions contributing to the encoding of sensory, emotional, attentional, evaluative and motivational aspects. This central itch matrix may be an interesting target for different therapies.

Itch is a complex and unpleasant sensory experience that induces the urge to scratch [1]. It is the most prevalent symptom of inflammatory skin diseases [2, 3] and difficult to be measured objectively. With its well-known psychophysiologic aspects, it has substantial impact on the quality of life of patients [4]. Its pathophysiology remains poorly understood in spite of numerous studies [2].

Quantity and quality of perceived itch show specific characteristics in different pruritic skin diseases. Clinical observations point to differences in the central nervous processing of pruritus. The multidimensional 'Eppendorf Itch Questionnaire' (EIQ) [5] was used in hospitalized patients suffering from atopic eczema (AE, n = 62) and chronic urticaria (CU, n = 58). Total scores (127 items), emotional and sensory ratings, reactive behavior and visual analogue scale (VAS) ratings for itch intensity were evaluated. The mean VAS ratings of itch intensity showed no significant difference between the two diseases. In contrast, the total EIQ score was significantly higher in the AE group with 231.6 ± 11.5 versus 175.2 ± 9.4. In 34 of 127 items, a significantly different rating was obtained, mostly with higher load for affective and some sensory items in AE. Significant differences were also seen in the description of the scratch response. Thus, itch perception in AE and CU differs on a qualitative level, influencing items relevant for quality of life. Similar findings were perceived in a study investigating the preventive effect of acupuncture on experimental itch – showing a preventive point-specific effect on the emotional items of the EIQ [6]. These findings accentuate the emotional component of the itch sensation; with possibly differences in CNS processing.

Itch can easily be elicited experimentally – most effectively via a histamine stimulus [7]. With its mainly subjective characteristics itch has some psychophysiological similarity to pain. Although some degree of overlap is present, recent neurophysiological studies have confirmed that itch pathways are clearly distinct from pain pathways [8–10]. In recent years, progress in central nervous system imaging technologies had substantial impact on itch research. New models to measure itch may also be useful for the development of new therapeutic strategies against pruritus.

Neuroimaging of Itch by Positron Emission Tomography

Objective covariates of itch and differences to pain processing were shown using imaging techniques for the CNS: a complex pattern of cerebral activation after experimental itch induction with histamine dihydrochloride (0.03 to 8%) at the right lower arm in healthy volunteers was observed in a $H_2{}^{15}O$ PET correlation study (n = 6) [8]. Subtraction analysis of histamine versus control condition revealed significant activation of the primary somatosensory cortex and motor-associated areas, predominantly left-sided activations of frontal, orbitofrontal and superior temporal cortex and anterior cingulate cortex. Compared to activation patterns induced by pain stimuli [11] itch did not lead to thalamus activation, but significant activation in the insula region and differences in sensory, motor and cingulate areas.

Mochizuki et al. [12] investigating the central modulation of histamine-itch by application of a contralateral cold pain stimulus, showed significant increases in regional cerebral blood flow in the anterior cingulate cortex, thalamus, parietal cortex, dorsolateral prefrontal cortex and premotor cortex.

These results give evidence for central nervous processing of itch, and clearly demonstrate differences to pain processing. Planning of a scratch response is mirrored by extensive activation of motor areas in the cortex, while other areas may be involved in emotional evaluation of pruriception.

New Methodology Enabling Itch Measurement by Functional MRI

Until recently functional magnetic resonance imaging (fMRI) studies on itch had been hampered by the lack of a phasic stimulus. In contrast to pain, no method had been described to elicit and stop the sensation of itch within seconds. In a recent study the itch sensation was investigated using a methodology with short term temperature changes for modulation of histamine-induced itch [13].

In 9 healthy right-handed male volunteers, 1% histamine dihydrochloride was used as the evaluated itch stimulus [5] on the right forearm with subsequent modulation of the target skin area temperature by a Medoc TSA thermode. The latter is capable of heating or cooling the skin and was placed exactly above the stimulus area. Using a boxcar design 14 equal cycles were applied: Each cycle started with a warm block producing a constant skin temperature of 32°C for 20 s then changing within 1.5 s (ramp 5°C/s) to a cold block of 25°C also lasting for 20 s.

Subjective scales were recorded using a computerized visual analogue scale (VAS) ranging from 0 to 100 at 4-second intervals. At one-third of the VAS (33/100) the intervention point 'scratch threshold' was installed. Above this threshold each individual felt the clear-cut desire to scratch; this, however, was not permitted nor done. Itch intensity was quantitatively expressed in percent of the maximum VAS value.

All subjects reported itch without pain within 40 s after histamine application. None of the volunteers felt pain sensation at any time during the course of the experiment.

In each individual subject as well as in the total group, significant differences between VAS rating intervals concerning itch intensity were noted. In each cycle itch intensity was generally perceived as higher during 25°C-blocks than during 32°C-blocks. Mean itch intensity was 50.6 ± 3.5% during the 25°C-block (intervals 6 to 10) and 33.8 ± 3.9% during the 32°C-block (intervals 1 to 5) with a highly significant difference ($p < 0.0001$) between the two temperature blocks (fig. 1).

Alternating changes in mean itch perception comparing warm and cold blocks were remarkably reproducible.

In spite of the common knowledge that intensive cold inhibits itch sensation, a reproducible, significant enhancement of histamine-induced itch by short-term moderate cooling was shown. This effect might be explained by peripheral and central adaptation processes triggered by abnormal afferent activity patterns.

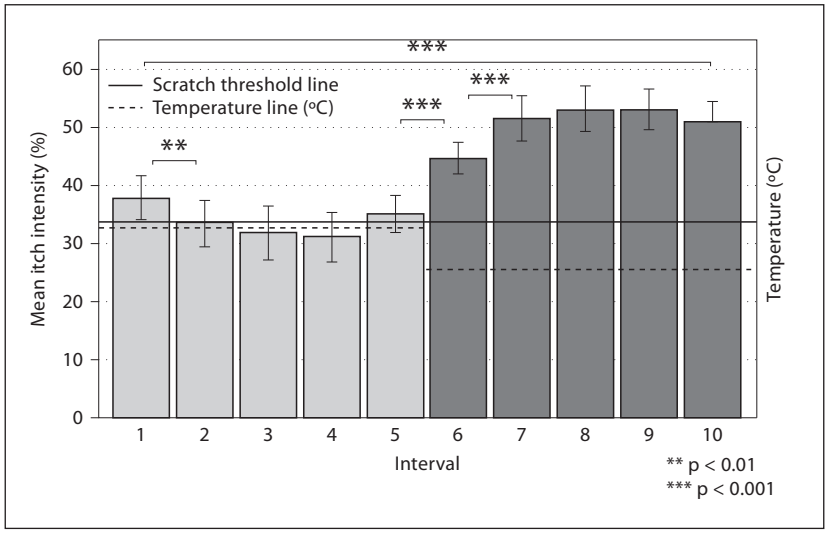

Fig. 1. Demonstrating increased itch intensity on lower temperature and in lesional compared to nonlesional skin as well as delayed onset of itch modulation in patients with atopic eczema. Mean itch intensity of both sessions at the various temperature intervals (n = 10). As indicated by the dotted line the red columns numbered 1 to 5 indicate warm temperature intervals (32°C), whereas the blue columns numbered 6 to 10 mark relatively cold temperature intervals (25°C), each lasting 4 s. Columns with horizontal line pattern represent healthy skin, columns with ascending line pattern represent nonlesional AE skin, columns with downward line pattern lesional AE skin. The yellow line represents the scratch threshold (33% itch intensity). Asterisks indicate selected significant differences between intervals. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. From Pfab et al. [21].

This method allows controlled and rapid modulation of itch. Short-term cooling enhances histamine-induced itch, providing the possibility of further and more detailed investigations of itch by functional imaging methods such as fMRI.

In a further study we evaluated this itch stimulus model in lesional (LS) and nonlesional (NLS) atopic eczema (AE) skin (n = 13, healthy skin (HS) of age-matched volunteers served as control (n = 9).). Thermal modulation was performed on a histamine stimulus in randomized order on LS or NLS in rapid alternating order from 32°C (warm) to 25°C (cold). Subjective itch ratings were recorded.

Mean VAS itch intensity was significantly ($p < 0.0001$) higher during the relative cold (55.2 ± 8.3% (LS); 48.6 ± 8.2% (NLS)) compared to the relative warm blocks (36.0 ± 7.3% (LS); 33.7 ± 7.6% (NLS)). Compared to HS the itch response was delayed in LS and NLS. Itch intensity was perceived highest in LS, followed by NLS and HS.

Moderate short-term temperature modulation led to a reproducible, significant enhancement of histamine-induced itch with the strongest effect in LS.

The differences in itch perception and itch kinetics between healthy volunteers and NLS in patients point towards an ongoing central inhibitory activity patients with AE, especially at the beginning of the itch provocation.

Cerebral Processing of Histamine-Induced Itch Using Short-Term Alternating Temperature Modulation – An fMRI Study

Using the previously established biphasic temperature stimulus model, we investigated the cerebral activation pattern of itch processing in 12 healthy volunteers with functional MRI [14].

Itch was provoked on the right forearm with 1% histamine-dihydrochloride. Local temperature modulation allowed reproducible itch provocation above scratch threshold (defined as 33/100 on a VAS) during 25°C whereas itch declined below scratch threshold during the 32°C stimulation period. No itch sensation was reported using 0.9% saline with temperature modulation.

The calculation of itch-specific activation maps for the first 4, 8, 12, 16 and 20 s of the 25°C stimulation period confirmed that the changes during the first 8 s are reflected by the higher brain activations during this time period than during the other time periods. Focusing on the first 8 s of 25°C stimulation, the thalamus, pre-SMA, lateral prefrontal cortex, anterior insular cortex and inferior parietal cortex were more active than during the saline condition ($p < 0.001$; fig. 2). The medial frontal cortex, orbitofrontal cortex, dorsal part of the anterior cingulate cortex (dACC) and primary motor cortex (M1) were all less active during histamine induced itch than during saline ($p < 0.001$; fig. 2).

So far this is the only imaging study on itch using a phasic supra-threshold itch model comparing itch and nonitch phases.

Further Neuroimaging Studies in Healthy Volunteers

Neuroimaging studies on itch have been performed using both PET [8, 12, 15–17] and more recently fMRI [18, 19]. Table 1 summarizes the findings of current neuroimaging studies.

Taking the results of these studies together key centers of histamine-itch perception in healthy volunteers seem to be ipsilateral pre-motor and supplementary motor area and contralateral cingulate cortex , insular cortex, thalamus and frontal inferior gyrus (inferior parietal and dorsolateral prefrontal cortex).

So far, one study [19] investigated the effect of allergen-induced itch in patients with mucosal atopy showing similarities to histamine itch (table 1). Mochizuki et al. [18] directly compared itch and pain stimuli with fMRI in healthy volunteers: Neural activity in the posterior cingulate cortex and the posterior insula associated with itch was significantly higher than that associated with pain; pain in contrast to itch, induced an activation of the thalamus correlating to pain sensation.

Leknes et al. [19] were the first to investigate the cerebral processing of allergen-induced itch, postulating a dysfunction of striato-thalamo-orbitofrontal circuits,

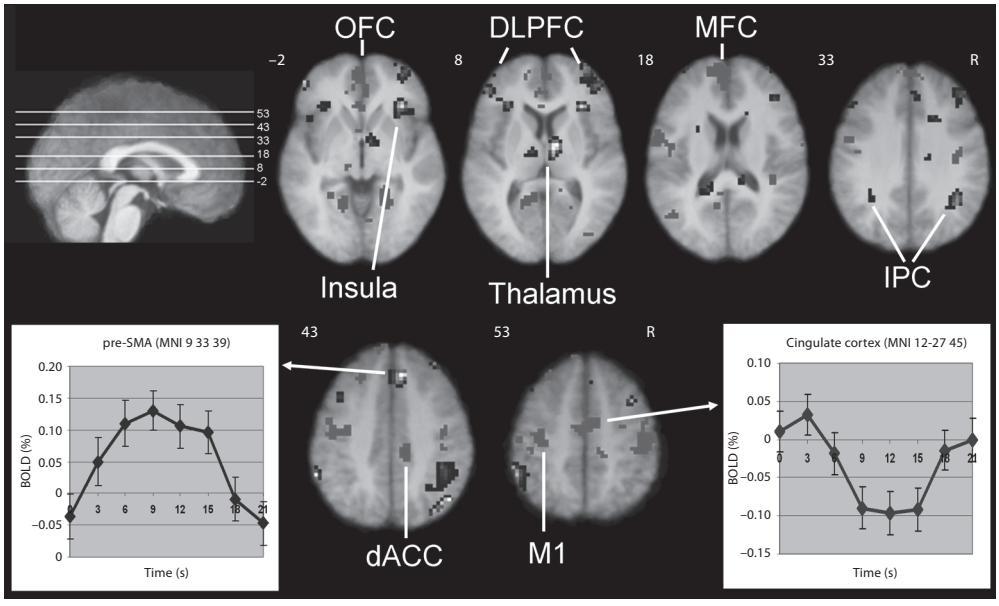

Fig. 2. Cerebral activation (red) and deactivation (blue) patterns induced by itch provocation: nonlesional skin of patients with atopic eczema, lesional skin of patients with atopic eczema, healthy control skin. Activation maps of histamine-induced itch compared to saline were calculated for the first 4, 8, 12, 16 and 20 s of the 25°C stimulation period and are superimposed on the averaged normalized T_1-weighted brain of all subjects. A dynamic process with increase and decrease of regional brain activation can be observed in the time course of the 25°C stimulation period. The statistical parametric maps were thresholded at $p < 0.005$. The right side of the image corresponds to right side of the brain (neurological convention). From Pfab et al. [21].

which are believed to underlie the failure to regulate the motivational drive in disorders associated with strong urges, e.g. addiction and obsessive compulsive disorder. Mochizuki et al. [20] investigated histamine-induced itch in 10 healthy volunteers using magnet encephalography (MEG) as well as fMRI suggesting the importance of the precuneus as well as premotor, primary motor, and anterior cingulate cortices (table 1).

Neuroimaging Studies in Patients Suffering Chronically from Itch

We characterized the cerebral responses in lesional skin (LS) and nonlesional skin (NLS) of 13 patients with atopic eczema (AE) using fMRI [21]:

Histamine-induced itch in NLS at 25°C stimulation was reflected by a deactivation of brain structures, such as the primary and secondary somatosensory, insular, cingulate and prefrontal cortex, supplementary motor area, premotor areas and basal ganglia. These deactivations were less pronounced in

the later course of 25°C stimulation with a parallel activation increase in the basal ganglia.

In contrast, histamine-induced itch in LS at 25°C stimulation was associated with an activation of the basal ganglia, insular cortex, prefrontal areas and parietal cortex. Deactivations were seen in the parietal, temporal, primary and secondary somatosensory, cingulate cortex, premotor and prefrontal areas, but were less robust than for NLS.

Our study supports a peripheral as well as a central component in the pathophysiology of chronic itch in patients suffering from atopic eczema. On the one hand, pathological skin conditions such as a skin barrier abnormality and local inflammation processes in atopic eczema patients [22, 23] point to a peripherally increased sensitivity to itch stimuli. On the other hand, central filter mechanisms might counteract this pathological skin condition to a certain point when the threshold of the pruriceptive input is exceeded.

Schneider et al. [24] demonstrated significant differences in central imaging of histamine-induced itch between patients with atopic dermatitis in non lesional skin and healthy subjects in a study correlating itch intensity with cerebral activation using PET.

Ishiuji et al. [25] recently compared itch induced by histamine-iontopheresis in lesional skin of 8 patients with AE compared to 7 healthy controls, showing significant differences between patients and healthy controls (table 1).

Key Anatomic Brain Regions of Itch and Their Function

Insular Cortex

The anterior insula is assumed to subserve subjective feelings [26] and to integrate sensory and emotional experiences [27]. It has been suggested that the insular cortex is part of an interoceptive system providing the basis for a cortical image of homeostatic activity that reflects all aspects of the physiological condition [28]. In this context, itch activation of the insular cortex might indicate an interference on homeostatic balance, leading to the desire to scratch [13, 19].

Pre-Supplementary Motor Area and Primary Motor Cortex, Motor Part of the Cingulate Cortex

The pre-SMA is thought to encode motor actions prior to self-initiated voluntary movements and during imagination of motor action [29]. M1 is typically involved in motor planning and execution highlighting the definition of itch which includes the intention to scratch [1]. As the subjects were not allowed to scratch the deactivation might indicate a suppression of motor activity. The dorsal anterior cingulate cortex (dACC) is also thought to be engaged in premotor planning [30, 31] as well as in stimulus intensity encoding [32, 33]. Translating this information from pain to itch

Table 1. Summarizing findings of current neuroimaging studiesActivation in the corresponding region is marked by I (ipsilateral) or C (contralateral); the minus (–) indicates reduced activation in comparison to a saline control stimulus.

	Healthy volunteers						
	Hsieh et al. [16], 1994	Drzezga et al. [15], 2001	Mochizuki et al. [12], 2003	Schneider et al. [24], 2008	Walter et al. [17], 2005	Leknes et al. [19], 2007	Valet et al. [14], 2007
Scanner	PET	PET	PET	PET	fMRI 1.5T	fMRI 3T	fMRI 1.5T
Neuroimaging analysis	subtraction	correlation	subtraction	correlation	correlation	correlation	subtraction
Itch induction	intracutaneous injection	skin prick model	lontophoresis	lontophoresis	skin prick model	skin prick model	skin prick model
Itch stimulus	histamine	histamine	histamine	histamine	histamine	histamine	histamine
Number of subjects	10	6	15	6	6	14	12
Brain region							
Primary somatosensory cortex (BA 1–3)		I,C		C			C-
Somatosensory associated/ parietal cortex (BA 5, 7)		I,C	I	C			
Primary motor cortex (BA 4)		C					
Pre-motor and supplementary motor cortex (BA 6)	I,C	I,C	I	C			I
Cerebellum	I,C				C		
Insular cortex (BA 13, 14)		C				I,C	C
Cingulate cortex (BA 23, 24, 25, 29, 30, 32)	C	I,C	C	C	C	I,C	I-
Prefrontal cortex (BA 9)	I,C	C		I			
Frontopolar and orbitofrontal area (BA 8, 10–12)		C			I,C		I-,C-
Inferior parietal and dorsolateral prefrontal cortex (BA 45, 46, 47)		C	I,C				I,C
Temporal gyrus (BA 20–22)					C		
Temporal lobe/Wernicke's area (BA 38–40)			I				I,C

				Atopic patients	Patients with atopic eczema			
Mochizuki et al. [18], 2007	Herde, 2007	Ishiuji et al. [25], 2009	Mochizuki et al. [20], 2009	Leknes et al. [19], 2007	Schneider et al. [24], 2008	Ishiuji et al. [25], 2009	Pfab et al. [21], 2010	Pfab et al. [21], 2010
fMRI 3.0T	fMRI 1.5T	fMRI 1.5T	fMRI 3T and MEG	fMRI 3T	PET	fMRI 1.5T	fMRI 3T	fMRI 3T
correlation	subtraction	correlation	correlation	correlation	correlation	correlation	subtraction	subtraction
iontophoresis	intracutaneous microdialysis	iontophoresis		skin prick model	iontophoresis	iontophoresis	skin prick model non-lesional skin	skin prick model lesional skin
histamine	histamine and codeine	histamine	electricity	histamine	histamine	histamine	histamine	histamine
14	10	8	10	14	8	8	13	13
	C	C		C			I-,C-	I-,C-
	C	C				I,C		I-,C-
		C		C			I-,C-	
I	I,C		I	C	I,C	I,C		I-,C-
	I,C		C		I,C			
C	I,C		I,C		I	I	I-,C-	I,C
C	I,C		C	I,C		I,C	I-,C-	I-,C-
	I,C				I		I-,C-	I,C
I	C			I,C	I	I,C		
	I,C		I			I,C		I,C
	I,C							I-,C-
	I,C	C	I,C	C	C			

Table 1. Continued

	Healthy volunteers						
	Hsieh et al. [16], 1994	Drzezga et al. [15], 2001	Mochizuki et al. [12], 2003	Schneider et al. [24], 2008	Walter et al. [17], 2005	Leknes et al. [19], 2007	Valet et al. [14], 2007
Thalamus			C			I,C	I,C
Basal ganglia						I	
SII (BA 40, 43)							
Precuneus (BA 7, 31)							
Putamen							
Visual association gyrus (BA 18)							
Anterior entorhinal cortex (BA 34)							

processing, we hypothesize that the dual function of the dACC, with the anatomically neighboring M1, is advantageous for the generation of an adequate motor response to the itching stimulus (planning of a scratch response).

Thalamus and Primary Somatosensory Cortex

The activation of the thalamus and S1 cortex can be attributed to sensory aspects of itch processing. The ability to localize itch (S1) plays an important role in the initiation of withdrawal behavior. These brain structures are fulfilling important functions regarding detection, localization, discrimination and intensity encoding of sensory stimuli [34].

Inferior Parietal Cortex and Dorsolateral Prefrontal Cortex

The inferior parietal cortex is known to be involved in the spatial representation of the intra- and extrapersonal space (body scheme) and regarded as polymodal association area integrating multisensory information from the thalamus, insula, anterior cingulate cortex and prefrontal cortex [35]. It is known that lesions of this region in the non-dominant hemisphere are highly associated with neglect and inattention syndromes. Activation of this region may therefore reflect a spatially directed attention to the itching stimulus.

The dorsolateral prefrontal cortex is associated with cognitive evaluative, attention-dependent, working memory and executive functions [36]. Besides input from the thalamus and cingulate cortex, it receives and processes multisensory information

				Atopic patients	Patients with atopic eczema			
Mochizuki et al. [18], 2007	Herde, 2007	Ishiuji et al. [25], 2009	Mochizuki et al. [20], 2009	Leknes et al. [19], 2007	Schneider et al. [24], 2008	Ishiuji et al. [25], 2009	Pfab et al. [21], 2010	Pfab et al. [21], 2010
	I,C		I	I,C	C			
I	I,C			I,C	I	C	I-,C-	I,C
			I,C					
		C	I			I,C		
						C		
						I,C		
						C		

mainly from the inferior parietal cortex [36]. The sensory convergence and integration is required in the preparation of motor action.

Conclusion

Itch sensation is processed by a network of brain regions contributing to the encoding of sensory, emotional, attention-dependent, cognitive-evaluative and motivational patterns. Patients with atopic eczema show different activation patterns and kinetics compared to healthy volunteers. It now seems possible to further analyze the specific effects of various therapies on these significant activation patterns.

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