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Invited review article

Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments

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Abbreviations:
ACC, anterior cingulate cortex; aIC, anterior part of the insular cortex; AD, atopic dermatitis; AT, autogenic training; BT, behavioral treatment; DE, dermatological education; DEBT, dermatological education plus behavioral treatment; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; IC, insular cortex; MEG, magnetoencephalography; MCC, midcingulate cortex; PET, positron emission tomography; PCC, posterior cingulate cortex; pIC, posterior part of the insular cortex; PM, premotor cortex; SI, primary somatosensory cortex; MI, primary motor cortex; PAR2, protease-activated receptors2; rTMS, repetitive Transcranial Magnetic Stimulation; SII, secondary somatosensory cortex; STT, spinothalamic tract; SMC, standard medical care; SMA, supplementary motor area; tDCS, transcranial Direct Current Stimulation

ABSTRACT

Atopic dermatitis (AD) is a common chronic skin disease that is characterized by intense pruritus and has high impairment of quality of life. AD is often described as “the itch that rashes, rather than the rash that itches”. Several studies suggest that mechanisms of central modulation play an important role in the development and maintenance of chronic itch. Therefore, treating the neurosensory aspects of itch is an important part in the management of chronic itch. However, little attention has been paid to the role of the central nervous system in the processing of itch in AD. Targeting itch-related anatomical structures in the brain with non-invasive treatments such as psychological interventions and transcranial Direct Current Stimulation (tDCS) could have an antipruritic effect in AD. Therefore, in this review article, we discuss the current progress in brain imaging research of itch, as well as the efficacy of non-invasive interventions for itch relief in this patient group.

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Introduction

Atopic dermatitis (AD) is a skin disease characterized by other atopic diseases in the patient and/or their family members, lichenification at certain sites of the body, and a chronically relapsing course.[1] Itch is a cardinal symptom of this skin disease[1] which bothers many patients in the evening and at night and can prevent the patients from falling asleep.[2] The response to an itch is usually scratching, which exacerbates inflammation through mechanical stimulation[3] and finally exacerbates itch. This leads to the development of a vicious cycle of itching and scratching. Feelings of unattractiveness, stigmatization, and depression are common phenomena in AD patients.[4,5] Thus, it is not surprising that patients with AD often report suffering from a reduced health related-quality of life.[6]

There are several studies that investigated the underlying physiological processes of AD itch. Many of these studies focused on genetic abnormalities, immunological dysfunctions, or deficiencies in the skin barrier function.[7] On the other hand, there are only a handful of studies focusing on the cerebral mechanisms of itch in patients with AD. Some studies report that psychological interventions are effective for chronic itch.[8] It was also reported that non-invasive brain stimulation interventions such as transcranial Direct Current Stimulation (tDCS) could reduce itch.[9] These studies suggest that the brain is an important target for the treatment of itch in AD. Therefore, in this article we review the current progress in neuroimaging research of itch, and discuss the efficacy of psychological interventions and non-invasive brain stimulation for itch relief.

The cerebral mechanism of itch

Human brain imaging studies of itch

The first study investigating the cerebral mechanism of itch was published in 1994.[10] Since then, several brain imaging studies have been conducted using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG).[10–20] Most of these studies have investigated the cerebral response to an itch stimulus using pruritogens (e.g., histamine, or cowhage) or electrical itch stimuli in healthy subjects. The somatosensory cortex, cingulate cortex, medial parietal cortex, insular cortex (IC), and motor cortex are considered to be key brain regions associated with itch perception and scratching (Fig. 1). Thus, these regions are discussed in detail in the following paragraphs.

Somatosensory cortex

The somatosensory cortex receives projections from the spinal cord through the thalamus. It is divided into two regions: One is the primary somatosensory cortex (SI), which is located in the post-central sulcus, the other is the secondary somatosensory cortex (SII), which is located within the upper part of the lateral sulcus in the region of the parietal operculum. Previous brain imaging studies have demonstrated that the SI and SII are activated by itch stimuli. In general, the somatosensory cortex is considered to be associated with perception of intensity and location of somatosensory input. In fact, the SI represents the sensory homunculus (i.e., a physical representation of the human body) and the SII also

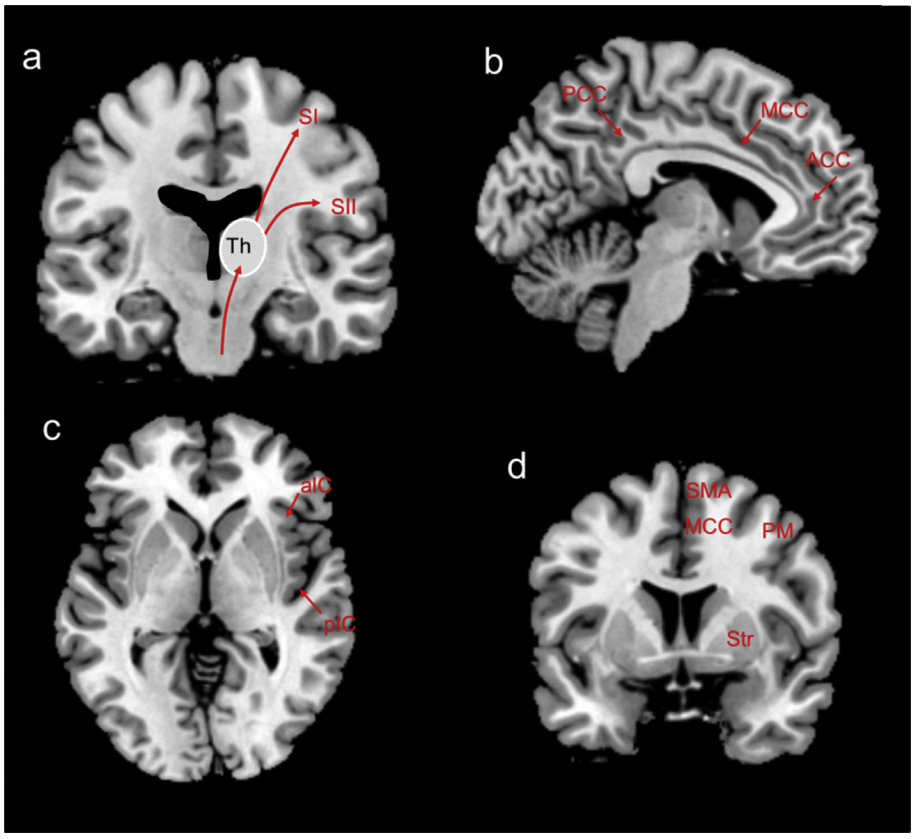

Fig. 1. Brain regions associated with itch. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; Th, thalamus; ACC, anterior cingulate cortex; MCC, midcingulate cortex; PCC, posterior cingulate cortex; aIC, anterior part of the insular cortex; pIC, posterior part of the insular cortex; SMA, supplementary motor area; PM, premotor cortex; MCC, midcingulate cortex; Str, striatum. MRI images: 2D images of the brain template implemented in the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/).

has a somatotopic map.[21] In previous brain imaging studies, the location of SI activation by itch stimuli corresponded to the arm area (site of the itch stimuli) of the homunculus. Drzezga *et al.* reported that activity in the SI positively correlated with the intensity of itch stimuli.[11] This was consistent with the results of other studies that found a linear relationship between the neural response of the SI and the intensity of the somatosensory stimuli.[22–26] The SII site did not show such a linear relationship. Activity in this region exhibited an S-shaped function with a sharp increase in amplitude only when a stimuli's intensity was well above the pain threshold.[22–26] Thus, some researchers consider that the SI plays a more important role for the intensity coding of somatosensory stimuli. However, it is still uncertain if the neural response of the SI represents the intensity of all perceived somatic sensations.

Cingulate cortex

The cingulate cortex can be divided into three regions: the anterior cingulate cortex (ACC), midcingulate cortex (MCC), and posterior cingulate cortex (PCC). In previous brain imaging studies of itch, robust activation was observed in the MCC or posterior part of the ACC during itch stimuli.[10–12,17,20] These regions are associated with cognition, motivation, and movement rather than emotional processing.[27,28] These activations in the cingulate cortex are likely to be associated with cognition/evaluation of itch stimuli and/or the urge to scratch.

Medial parietal cortex

The medial parietal cortex including the precuneus and PCC is located on the inside between the two cerebral hemispheres (Figs. 1 and 2). Previous brain imaging studies of itch frequently observed activation of the medial parietal cortex.[13,17,19,20,29] This region may be selective for itch, as it is less sensitive to other somatosensory stimuli, including tactile and painful stimuli.[30] It was reported that pain sensitivity is inversely related to regional grey matter density in the medial parietal cortex.[31] In addition, it was reported that activity in the medial parietal cortex was modulated during the modulation of pain by hypnosis, speculating that this region may partly be involved in this analgesic effect.[32,33] An fMRI study of itch reported that activity in the precuneus is significantly and positively correlated with subjective sensations of itch.[17] Considering these findings, the medial parietal cortex may be associated with the subjective sensations of itch and pain. The medial parietal cortex is associated with memory and attention.[34] These psychological factors may influence itch and pain sensations.

Insular cortex

The anterior and posterior ICs have different roles. The anterior part is considered to be more engaged in awareness of emotion and subjective feelings, whereas the posterior part is considered to be associated with awareness of affective body feelings (e.g., pain, cold, thirst).[35] Lesions in the anterior part of the IC (aIC) lead to deficits of emotional awareness (e.g., alexithymia),[36] and lesions in the posterior part of the IC (pIC) induced a loss of bodily feelings (e.g., anosognosia)[37] and abnormal bodily feelings, such as spontaneous pain.[38] An fMRI study showed that subjective feelings of perceived thermal sensations and physical stimulus intensity of the thermal stimuli were significantly correlated with activity in the aIC and pIC, respectively.[39] Previous itch studies observed activations of both parts of the ICs during itch stimuli.[13,14,16,17,20] The pIC is one of the major cortical targets of the spinothalamic tract (STT),[40] which transmits itch signals to the brain.[41,42] In accordance with this anatomical pathway, only the pIC showed a significant correlation between its activity and the physical intensity of itch stimuli.[11] On the other hand, several studies reported that activity in the aIC was significantly and positively correlated with the subjective itch sensation and unpleasantness of itch.[13,16,17,20,27]

Motor cortex

The motor cortex (motor-related cortical areas) including the supplementary motor area (SMA), premotor cortex (PM), and primary motor cortex (MI) are activated by itch stimuli. Interestingly, these activations are independent of a scratching response, as no movements were allowed to subjects during PET or fMRI measurements. Simply imagining movement induces activation of the motor cortex.[43,44] In addition, human EEG and animal

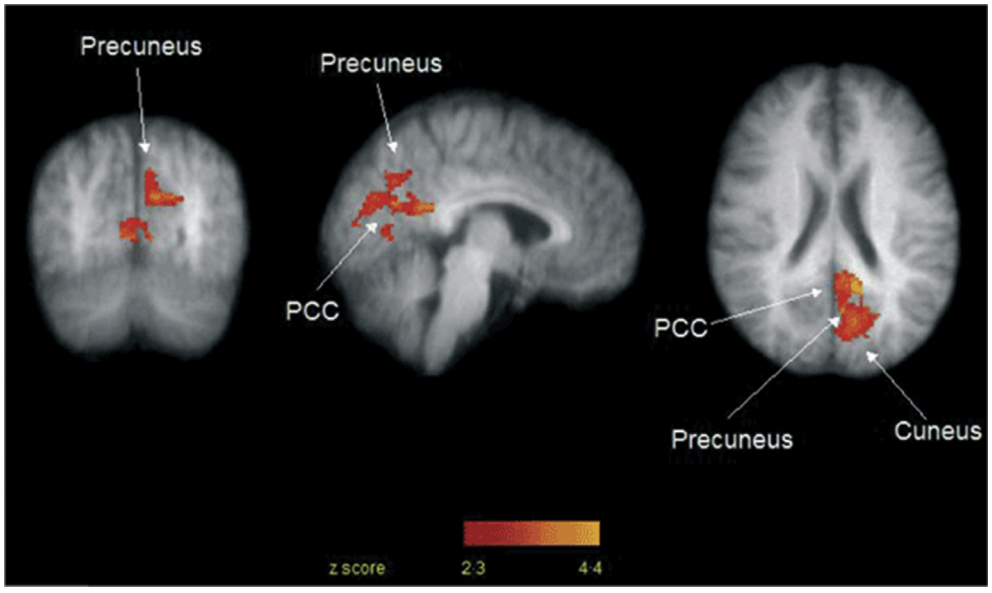

Fig. 2. Comparison of brain activity during itch stimuli between AD patients and healthy controls. The medial parietal cortex, including the posterior cingulate cortex (PCC) and (pre-)cuneus, exhibited a significantly higher reaction to itch stimuli in the AD patient group when compared with the healthy control group. This figure is adapted from the article by Ishiuji *et al.* published in British Journal of Dermatology.[19]

electrophysiological studies have demonstrated that the motor cortex is activated a few seconds before motor initiation, which is known as “readiness potential” or “Bereitschaftspotential”.[45–47] Based on these findings, the motor cortex is considered to be associated not only with motor execution, but also with its preparation. The motor cortex has anatomical connections with the striatum, which is also activated by itch stimuli and plays an important role in motivation and motor control. Co-activations of these regions during itch stimuli may reflect both motor preparation for scratching and urge to scratch.

Histaminergic vs. non-histaminergic itch

The major ascending pathway to mediate itch sensations is the STT, which can be divided into two pathways. One is a histaminergic pathway and the other is a non-histaminergic pathway. The non-histaminergic pathway has protease-activated receptors2 (PAR2) that can be exogenously stimulated by spicules of cowhage (*Mucuna pruriens*).[48] The itch sensation transmitted by these pathways activates common brain regions including the SI, SII, IC, thalamus, and motor-related regions. Of note, cowhage evokes a more extensive activation of the IC, claustrum, globus pallidus, caudate body, putamen, and thalamic nuclei on the contralateral side of the stimuli (Fig. 3).[20] These differences may be related not only to an intrinsic specificity in cortical projection, but also to the fluctuating quality and associated nociceptive signaling (e.g., stinging, burning) elicited by cowhage. These sensations are frequently reported in many cases of chronic itch in AD.

Brain activity in AD patients

As outlined above, there are several studies that investigated which brain areas are activated during itch. Only two studies have investigated the similarities and differences in brain activation patterns associated with itch between AD patients and healthy subjects. Overall, itch induction in AD patients resulted in a more diffuse pattern of activation when compared to healthy subjects.[49] One of the studies was able to show a positive correlation between disease severity (as measured by a standardized clinical measure; EASI score) and activations of the ACC and dorsolateral prefrontal cortex (DLPFC).[19] Furthermore, this study reported an overreaction to itch stimuli in the medial parietal cortex of AD patients (Fig. 2). The medial parietal cortex is associated with memory[34] and AD patients have many experiences of severe itch in their lives, which would be deeply ingrained within the memory system in the brain. Perhaps, past itch experiences are unconsciously or consciously retrieved, which modulates (i.e., enhances) subjective itch sensations. In fact, AD patients perceive a real itch sensation even when they watch scratching behavior of others, with the response being significantly more robust in comparison to healthy controls.[50] In a pain study, it was reported that pain hallucination is partly associated with activation of the medial parietal cortex, speculating that the memory system may have a capability to create real somatic sensations.[51]

The other study comparing AD brain activity to healthy controls, reported significantly higher activity in the basal ganglia, including the striatum, for patients with AD.[18] Also, a study investigating the difference in brain activity after evoked itch in nonlesional versus lesional skin of AD patients found the basal ganglia to be significantly activated after histamine-induced itch was induced on lesional skin.[52] Activation in the basal ganglia is associated with motivation and craving. An over activity in this region could possibly explain the excessive, pathological scratching commonly seen in AD patients. Other fMRI study also investigated the underlying cerebral mechanism of this phenomenon by comparing

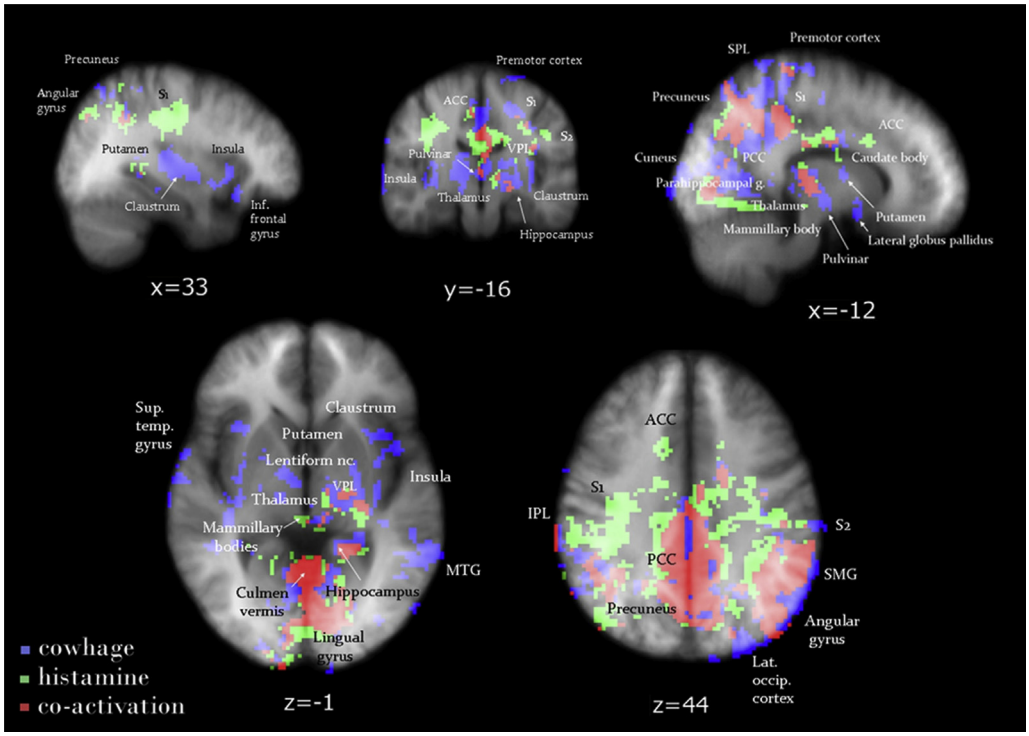

Fig. 3. Brain activity during histaminergic- and nonhistaminergic-itch stimuli in healthy individuals. Red: The overlap of brain activations, Blue: Nonhistaminergic itch (cowhage), Green: Histaminergic itch. ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; SPL, superior parietal lobule; M1, primary motor cortex; S1, primary somatosensory area; SMG, supramarginal gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; S2, secondary somatosensory area; VPL, ventral posterior lateral nucleus (of thalamus). This figure is adapted from the article by Papoiu *et al.* published in Neuroimage.[20]

brain activity during scratching between chronic itch patients and healthy controls.[53] In this study, the subjects themselves scratched the skin where cowhage-induced itch was evoked. Motor-related regions such as the SMA, PM, MI, and MCC were significantly activated during scratching in both groups. However, activity in these regions was significantly higher in the patient group, which included several AD patients (Fig. 4a). A similar result was also observed even when the skin was scratched in the absence of itch (Fig. 4b). In addition, the intensity of activity in motor-related regions during scratching was significantly and positively correlated with the intensity of pleasurable sensations in the patient group. This significant positive correlation suggested that scratching-induced pleasurability augmented activity in motor-related regions irrespective of whether the skin was itchy or not. The enhanced activity in motor-related regions may drive excessive scratching, seen in chronic itch patients. Another interesting finding was that an intense pleasurable sensation was evoked by scratching the skin even in the absence of itch in the patient group. In contrast, scratching the skin without itch does not induce pleasurable sensations in healthy subjects. Thus, scratching is pleasurable for chronic itch patients, even in the absence of itch, and this could be one of the reasons why these patients frequently scratch their skin.

The duration of chronic itch and scratching may also have induced abnormalities. MRI studies with chronic pain and end stage renal disease pruritus patients have demonstrated structural changes in brain regions involved in pain and itch processing, respectively.[54–56] Considering these studies, long term suffering from chronic itch may induce not only functional, but also structural abnormalities in AD patients, which could possibly be affected by non-invasive treatment like psychological interventions.

Psychological interventions as treatment of itch in AD

A few studies summarized which psychological interventions had positive effects on itch and scratching in AD patients.[57,58] Ehlers *et al.* compared the effects of four different interventions on itch and scratching in AD patients.[8] Patients either received

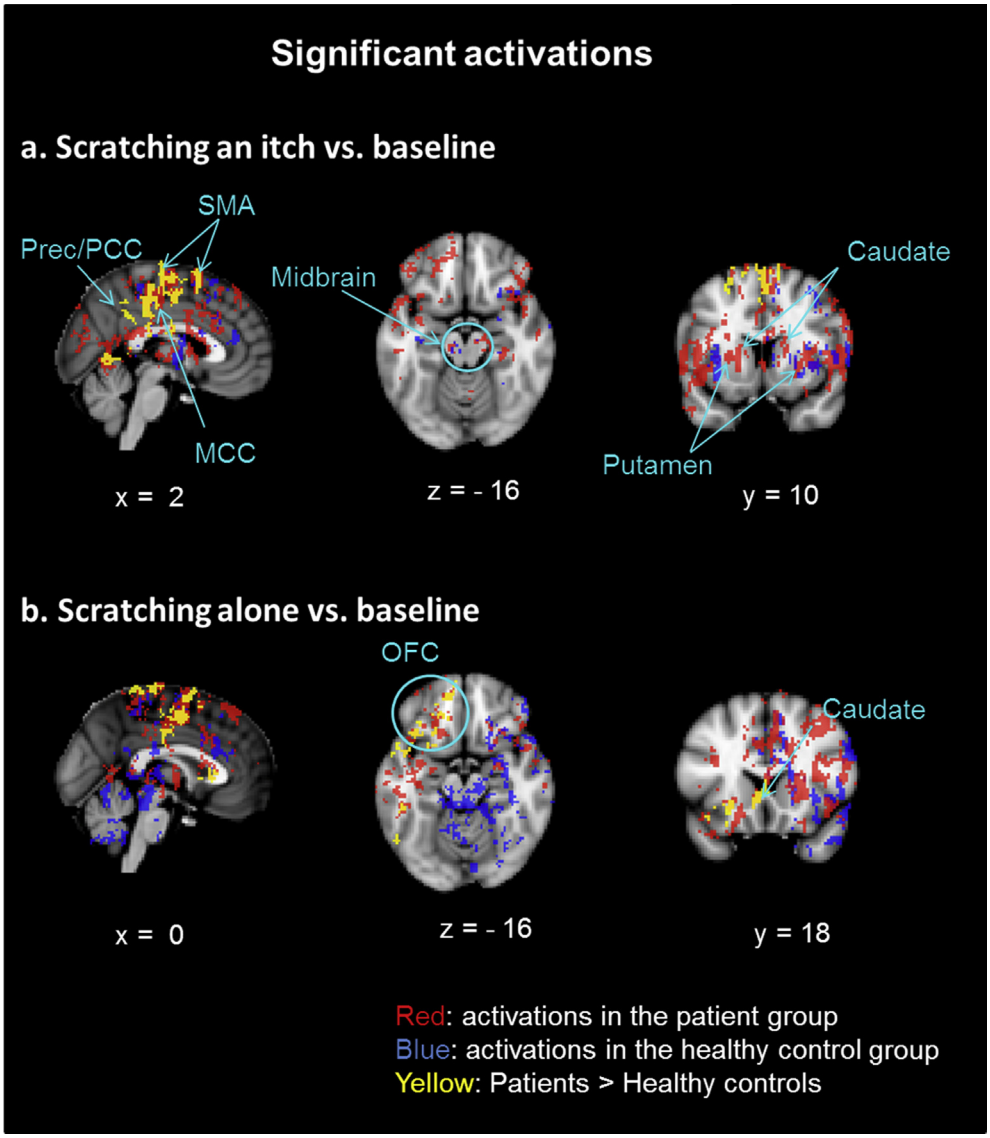

Fig. 4. Active scratching-induced activations in the brain. Brain regions significantly activated during scratching an itch **(a)** and during scratching the skin in the absence of itch **(b)**. Prec, precuneus; PCC, posterior cingulate cortex; SMA, supplementary motor area; MCC, midcingulate cortex; OFC, orbitofrontal cortex. This figure is adapted from the article by Mochizuki *et al.* published in Journal of Investigative Dermatology.[53]

dermatological education (DE), autogenic training (AT), behavioral treatment (BT), dermatological education plus behavioral treatment (DEBT), or standard medical care (SMC). Each intervention lasted 12 weeks with weekly sessions, which took about 1.5–2 h each. Patients of all four groups showed an improvement in itch and scratching one year after treatment, when comparing to the pre-treatment values. Moreover, results indicated that patients of the DEBT group reported larger reductions in the frequency of itch and scratching than patients of the AT- or DE-groups. Evers *et al.* conducted a study, in which they investigated the effects of a multidisciplinary itch-coping program on itch, scratching, and the intake of itch-relieving medication immediately after treatment, as well as three and twelve months after treatment.[59] The study included 61 adult AD patients who took part in the program and 30 patients who were members of a waiting-list-control group. The intervention group participated in four 2-h sessions, in which self-monitoring techniques of itch and scratching, itch- and scratch triggering factors, as well as coping strategies and habit-reversal techniques were discussed. A booster session, which took place one month after the last session, was conducted to discuss long-term goals and how to prevent relapse. Immediately after the end of the training, as well as during the 3- and 12-month follow-up, the patients of the intervention group reported significantly less itch and scratching (divided into conscious scratching, automatic scratching and scratching at night) than the waiting-list-control group. In another study by Bae *et al.*, 25 AD patients were randomly assigned to either a control group or an intervention group that conducted a progressive muscle relaxation training at home twice a day for four weeks.[60] After the training, the intervention group displayed a significant reduction in itch, while the itch intensity in the control group was unchanged.

As these studies do not investigate the effects on brain activity it may be possible to learn from studies of patients with chronic pain given the similarities between chronic pain and chronic itch.[61] A recently published review nicely summarizes the effects of psychological interventions on brain mechanisms in chronic pain patients.[62] There are several studies that found different kinds of psychological interventions like cognitive behavioral therapy, meditation, or biofeedback lead to functional and structural changes of the brain in patients with chronic pain. Lackner *et al.* conducted one of the first studies on the effects of pain modulation through psychological interventions on brain mechanisms.[63] They were able to demonstrate that patients with irritable bowel syndrome benefited from group cognitive therapy aiming to reduce gastrointestinal symptoms and stress by identifying and replacing maladaptive, catastrophizing disease-related thoughts. In this study patients displayed a reduced activity in the parahippocampal gyrus and right ACC after treatment.

In addition to cognitive therapy, practicing mindfulness has also been shown to be associated with distress in patients with skin diseases[64] and at the same time to reduce pain[65,66] and affect brain structures in chronic pain patients.[67] Mindfulness relates to focusing on the current moment and includes the notions that the body and the surroundings are perceived, and that one's own feelings and thoughts are observed and accepted without being judged.[68] Studies using mediation, similar to mindfulness, showed that expert meditators had a different response to pain stimuli than those without experience in meditation.[69] In expert meditators the experience of pain stimuli was accompanied with an increased activity of the "salience network", which according to Lutz *et al.* comprises the left aIC and the anterior part of the MCC.[69] Besides differences in functional brain activity, meditators also displayed a lower sensitivity to pain that was related to thicker cortex in the right dorsal ACC, hippocampal formation, SII, and IC.[67]

In future, randomized, controlled studies it would be of great interest to investigate the effects of psychological interventions like CBT, mindfulness based stress reduction (MBSR), or relaxation on brain activity in patients with chronic itch. One could assume that a different attitude towards symptoms, which can be evoked by MBSR, would lead to a deactivation of cognition-related activity of the ACC or MCC during itch. On the other hand, other psychological approaches aiming to reduce scratching, like habit-reversal training, might not go along with a deactivation of motor-related regions like the SMA, since the urge to act ("Bereitschaftspotential") would still be there and only the following scratch response would be changed through the training. Furthermore, it is reasonable to assume that psychological interventions aiming to reduce stress would also have a positive effect on itch and alter the activity of itch-related brain structures, such as the ACC or IC.

Non-invasive brain stimulation as treatment of itch in AD

Another treatment option for chronic itch may be non-invasive brain stimulation, such as repetitive Transcranial Magnetic Stimulation (rTMS) and tDCS. Using these techniques one can manipulate neural activity in a human brain by applying weak magnetic or electrical stimuli through the scalp. These techniques are considered safe, with minimal side effects. Many studies have been done to investigate the effect of rTMS or tDCS on experimentally induced pain in healthy subjects, as well as in those suffering from chronic pain.[70–76] These studies have demonstrated that rTMS and tDCS have an analgesic effect by modulating activity in brain regions involved in pain processing. Considering the similarity of the mechanisms between pain and itch, non-invasive brain stimulation may also be able to reduce chronic itch. However, the efficacy of tDCS and rTMS for itch relief has been inadequately investigated. The effect of a tDCS intervention on experimentally induced acute itch (histamine-induced itch) was first investigated in 2015.[9] In this study, electrodes of tDCS were placed over the sensorimotor cortex (mainly the SI) and an electrical current of 1 mA was applied for 15 min. This study found a significant reduction of the itch sensation during the tDCS intervention. Similar to studies investigating the effect of a tDCS intervention on experimentally induced acute pain, the effect size was not large (e.g., 25% reduction). These studies applied tDCS only once to evaluate the analgesic and antipruritic effects. On the other hand, clinical studies showed significant analgesic effects on chronic pain and reported approximately 50% reductions in chronic pain from several days to several weeks.[75,77] Unlike other studies on experimentally-induced pain, clinical studies employed repeated application (e.g., 5–10 days) of tDCS.[72,75,77–79] Thus, we expect that repeated application of tDCS might be important in order to observe clinically meaningful antipruritic effects. In fact, a case report described that a tDCS intervention over the primary somatosensory or motor cortex for 5 consecutive days induced a clinically meaningful antipruritic effect in a patient with chronic itch due to neuropathy.[80] A potential mechanism behind itch relief by tDCS intervention over the SI may be that it modulates itch-related processing in the brain, since the SI has anatomical connections to the SII, striatum, and thalamus. However, as of yet, no study has investigated the underlying cerebral mechanism of itch relief by tDCS targeting the SI or MI.

Conclusion

AD is a chronic skin disease of intense itch and scratching. Imaging studies have found functional and structural abnormalities in brain areas associated with itch-related processing. As there are few studies that imaged the brain in atopic eczema patients future studies should further investigate the brain processing of itch and

scratching in AD. Moreover, in order to compliment the immune mediated treatments, AD patients should receive, non-invasive and non-pharmacological treatments, such as psychological interventions, rTMS, or tDCS, which can attenuate brain processing of itch.

Conflict of interest

The authors have no conflict of interest to declare.

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