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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

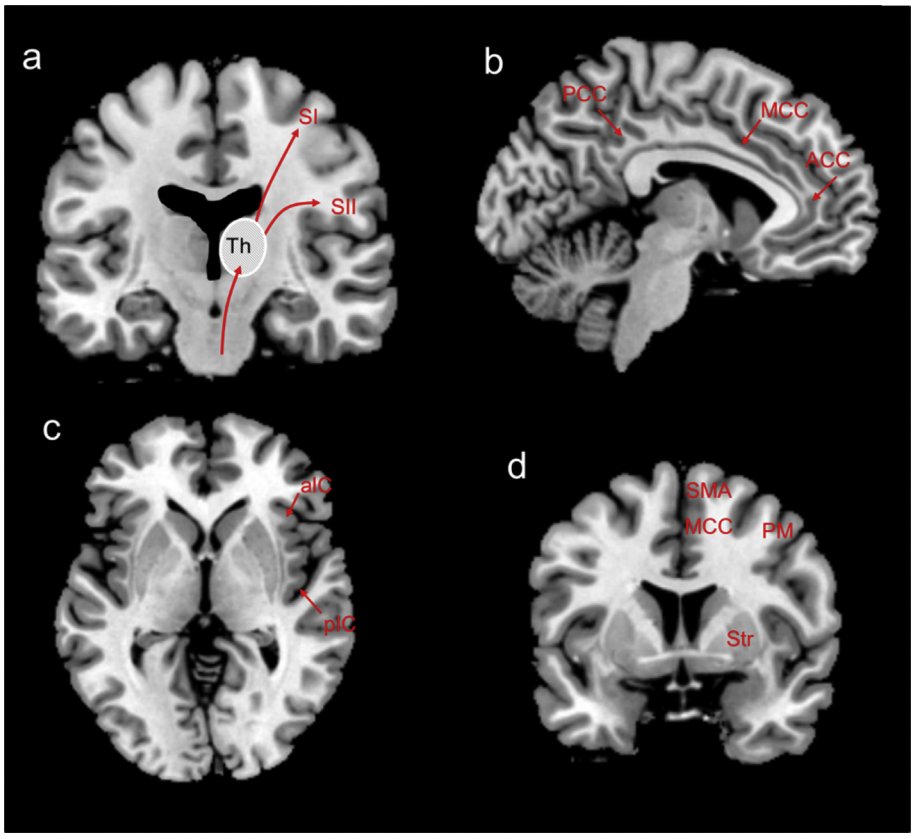

Fig. 1. Brain regions associated with itch. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; Th, thalamus; ACC, anterior cingulate cortex; MCC, midcingulate cortex; PCC, posterior cingulate cortex; aIC, anterior part of the insular cortex; pIC, posterior part of the insular cortex; 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/).