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Evoked itch perception is associated with changes in functional brain connectivity

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ABSTRACT

Chronic itch, a highly debilitating condition, has received relatively little attention in the neuroimaging literature. Recent studies suggest that brain regions supporting itch in chronic itch patients encompass sensorimotor and salience networks, and corticostriatal circuits involved in motor preparation for scratching. However, how these different brain areas interact with one another in the context of itch is still unknown. We acquired BOLD fMRI scans in 14 atopic dermatitis patients to investigate resting-state functional connectivity before and after allergen-induced itch exacerbated the clinical itch perception in these patients. A seed-based analysis revealed decreased functional connectivity from baseline resting state to the evoked-itch state between several itch-related brain regions, particularly the insular and cingulate cortices and basal ganglia, where decreased connectivity was significantly correlated with increased levels of perceived itch. In contrast, evoked itch increased connectivity between key nodes of the frontoparietal control network (superior parietal lobule and dorsolateral prefrontal cortex), where higher increase in connectivity was correlated with a lesser increase in perceived itch, suggesting that greater interaction between nodes of this executive attention network serves to limit itch sensation via enhanced top-down regulation. Overall, our results provide the first evidence of itch-dependent changes in functional connectivity across multiple brain regions.

1. Introduction

The brain circuitry supporting itch sensation is an active topic of research. While numerous studies have investigated and described pain-related brain mechanisms (Apkarian et al., 2005; Henry et al., 2011), much less is known about the brain circuitry involved with itch in spite of the clinical relevance of this highly debilitating symptom, which is present across multiple chronic itch conditions (Yosipovitch et al., 2003). Moreover, recent studies suggest that pain perception is associated with altered resting-state functional brain connectivity, which refers to stereotypical patterns of co-activation across multiple brain regions that show both trait and pain-state specificity (e.g., Napadow et al., 2010; Napadow et al., 2012; Loggia et al., 2013; reviewed in Fomberstein et al., 2013). However, itch-related functional brain connectivity, especially in chronic itch patients, has never been reported.

Atopic dermatitis (AD), also known as atopic eczema, is a pruritic chronic inflammatory disease of the skin, affecting approximately 17.8 million persons in the United States, in which patients experience highly debilitating itch (Finlay, 2001; Lapidus, 2001; Yosipovitch et al., 2003; Berke et al., 2012). Previous studies indicate that AD involves not only peripheral sensitization for itch (Lee and Yu, 2011; Rahman et al., 2011) but also central sensitization, in an analogous fashion as central sensitization for pain in chronic pain patients (Koltzenburg, 2000), such that stimuli that are perceived as painful in healthy subjects are

Abbreviations: aMCC, anterior mid-cingulate cortex; AD, atopic dermatitis; ASL, arterial spin labeling; BA, Brodmann area; BOLD, blood-oxygen-level dependent; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; ECG, electrocardiography; fcMRI, functional connectivity magnetic resonance imaging; fMRI, functional magnetic resonance imaging; GLM, general linear model; ITCH, evoked itch resting-state scan; L, left; MNI, Montreal Neurological Institute; MR, magnetic resonance; PCC, posterior cingulate cortex; PET, positron emission tomography; PMC, premotor cortex; pMCC, posterior mid-cingulate cortex; R, right; REST, baseline resting-state scan; S1/M1, primary sensorimotor cortex; SCORAD, SCORing atopic dermatitis scale; SPL, Superior parietal lobule; VAS, visual analog scale; vlPFC, ventrolateral prefrontal cortex.

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experienced as itching in AD patients (Ikoma et al., 2004; Ikoma et al., 2006; Schmelz, 2010). Not only specific allergens, but also stress and psychosocial factors, can exacerbate AD symptoms (Gil and Sampson, 1989; Koblenzer, 1999; Rahman et al., 2011). This complex symptomatology, and its bidirectional relationship to stress and psychosocial factors, which can be both a cause and a consequence of itching and scratching (Gil and Sampson, 1989; Lapidus, 2001; Arck and Paus, 2006; Chida et al., 2008; Mizawa et al., 2013; Yaghmaie et al., 2013; Schut et al., 2014), point to an essential role of the central nervous system in AD (Ikoma et al., 2004; Misery, 2011; Pfab et al., 2012a; Darlenski et al., 2014).

In healthy subjects, a number of studies indicate that experimentally-induced itch activates a brain network which includes pre-motor and supplementary motor area, thalamus, and cingulate, insular, inferior parietal, and prefrontal cortices (reviewed in Pfab et al., 2012a). However, few studies have investigated the brain circuitry supporting itch in AD. Studies from our group and others suggest that brain response to experimentally induced itch in AD differs from healthy subjects, consistent with abnormal itch sensitivity in AD (Ikoma et al., 2004; Schneider et al., 2008; Ishiuji et al., 2009; Pfab et al., 2010; Pfab et al., 2011; Pfab et al., 2012b; Napadow et al., 2014). In a recent functional MRI (fMRI) study, we evoked clinically-relevant itch in AD patients by using individually-matched allergens and our validated temperature-modulated itch induction procedure (Napadow et al., 2014). In this procedure, a thermode is used to modulate skin temperature between 32 °C (warm) and 25 °C (cool), in 20-s blocks (Pfab et al., 2006). This procedure has reliably been used to experimentally modulate itch, such that cooling the skin gradually increases itch sensation over the first 10 s, followed by a phase in which itch sensation reaches a peak plateau (Pfab et al., 2006; Pfab et al., 2010). We found that different brain regions were activated during these different phases of itch induction (i.e., increasing itch and peak itch plateau). During the increasing itch phase, the right anterior insula, right anterior middle cingulate cortex, bilateral striatum (putamen and caudate), right globus pallidus, and right ventrolateral prefrontal cortex were activated. Conversely, during the peak itch plateau phase the right dorsolateral prefrontal cortex, bilateral premotor cortex, and left superior parietal lobule were activated. Notably, reduction of itch after non-pharmacological (acupuncture) therapy was associated with reduced activation in the putamen and right anterior insula (Napadow et al., 2014), further highlighting the important role of these regions in itch processing.

In the present study, we investigated functional brain connectivity before and after experimentally inducing (or exacerbating) itch, using allergen skin prick in nonlesional skin while AD patients were resting in the MRI scanner. We used functional connectivity magnetic resonance imaging (fcMRI) with seed-based correlation methods to evaluate changes in functional brain connectivity associated with itch. To our knowledge, this is the first study to investigate how functional brain connectivity is modulated by itch, particularly the clinically-relevant itch state — a common cause of suffering in AD patients.

2. Materials and methods

2.1. Study participants

Patients aged 18–60 with a clinical diagnosis of AD and a score greater than 18 on the SCORing Atopic Dermatitis (SCORAD) scale (European Task Force on Atopic Dermatitis 1993; Schmitt et al., 2013) were enrolled. Recruitment was by print and e-mail advertisement as well as referrals from physician colleagues in the Department of Dermatology at the Massachusetts General Hospital. Volunteers who met eligibility criteria via phone screening were invited to a preliminary session in the laboratory during which a licensed dermatologist (F.P.) assessed their eligibility to the study via medical examination and focused history. In addition, eligible participants had to show type-I sensitivity to grass pollen and/or dust mites, as demonstrated by wheal and flare formation upon skin prick testing. For each participant, the most effective itch-inducing allergen was determined among Timothy grass pollen (100,000 bioequivalent allergy units per milliliter) and the two most common types of house dust mites in North America and Europe (*Dermatophagoides pteronyssinus*,10,000 allergy units per milliliter, and *Dermatophagoides farinae*,10,000 allergy units per milliliter, Allergy Laboratories, Oklahoma City, OK). Participants also completed the Edinburgh Inventory for handedness (Oldfield, 1971). The study protocol was approved by the Human Research Committee of Massachusetts General Hospital and all study participants gave informed consent. Participants were required to stop all immunosuppressive medications at least 10 days prior to the study to avoid potential suppression of itch perception.

2.2. Data acquisition

As part of a previously published study of the anti-pruritic effects of acupuncture (Napadow et al., 2014), each patient took part in an initial clinical screening session followed by two separate fMRI sessions (at least 1 week apart) during which resting-state scans were performed before and after allergen itch induction (but before any verum or placebo treatment was applied), with corresponding self-report ratings of perceived itch. The baseline resting-state scan (REST) occurred at the beginning of the session. The allergen-evoked itch resting-state scan (ITCH) was performed 15–17 min after allergen skin prick, within the period of time when allergen induced itch sensation is known to persist after skin prick (Pfab et al., 2010). A single drop of the most pruritogenic allergen (as determined during the clinical screening session) was applied on a non-lesion site on the left volar forearm. The skin was then punctured with a plastic MR-compatible lancet (Duotip Test II, Lincoln Diagnostics, Decatur, IL) such that the allergen solution was deposited at the dermal–epidermal junction, where the terminals of itch-related C-fibers are located (Shelley and Arthur, 1957). Using this procedure, an itch sensation develops with a median latency of 35 s and persists more than 15 min after application (Pfab et al., 2010). An absorbent gauze pad was then used to carefully remove the drop of allergen solution 120 s after application. With this method, the skin puncture is sufficiently shallow to avoid sustained pain, as previously reported (Pfab et al., 2006), and can be considered an induction of pure itch rather than a combination of itch and pain.

Brain imaging was performed on a Siemens Trio 3 Tesla MRI scanner (Siemens AG, Erlangen, Germany) with vendor-supplied 32-channel multi-array head coil. A high-resolution T1-weighted anatomical scan was collected using an isotropic multi-echo MPRAGE pulse sequence (TR/TE1/TI = 2530/1.64/1200 ms, 256 × 256 matrix, 256 mm field-of-view (FOV), 7° flip angle) (van der Kouwe et al., 2008). Functional imaging (BOLD fMRI) was performed using a gradient echo T2*-weighted pulse sequence (TR/TE = 2 s/30 ms, 32 anterior commissure–posterior commissure (AC—PC) aligned slices, slice thickness 3.6 mm, 64 × 64 matrix, 200 mm FOV, 90° flip angle). Each resting-state fMRI scan had a duration of 6 min (180 time points). Electrocardiography (ECG) and respiratory activity were simultaneously recorded throughout the scans using a Powerlab system (ML880, ADInstruments, Colorado Springs, CO) at a 400 Hz sampling rate. ECG data were acquired and filtered using an MR-compatible physiological monitor (Magnitude 3150 MRI Patient Monitor, In vivo, Gainesville, Florida) designed to minimize radio frequency and gradient switching artifacts generated during the MRI scan. Respiratory data were collected using a custom-built system based on that devised by Binks et al. (2007) which consists of two MR-compatible pneumobelts placed around the chest and abdomen and connected to air pressure transducers (PX138-0.3D5V, Omegadyne, Inc., Sunbury, Ohio).

Immediately before the baseline scan and immediately after the induced-itch scan, subjects were asked to rate the intensity of experienced itch on a visual analog scale (VAS) from 0 (no itch) to 100 (most intense itch imaginable), with 33 corresponding to an “urge to