Brain Activation by Histamine Prick Test-Induced Itch

To the Editor:

Itch is a well-known dermatological symptom whose reactions in the brain have been studied very less. In a study with functional magnetic resonance imaging (fMRI) response to histamine iontophoresis, McGlone et al. (2001) showed that the forebrain regions activated by brief itch (3–4 min) are different from those activated by pain. These findings provide insights into separate motivational and behavioral consequences of itch and pain. In previous studies, Darsow et al. (2000) and Hsieh et al. (1994) could also identify functional covariates of the itch sensation in the central nervous system by positron emission tomography (PET) analysis. A co-activation of the anterior cingulate cortex, supplementary motor area, premotor area, and inferior parietal lobe was found. Somatosensory areas were significantly activated only in one study (Darsow et al., 2000). All the studies reported above either used stimulation evoking short-lasting itch or recorded brain activation in a short time frame (e.g., 50 s). To our knowledge, there are no studies examining brain activations during the course of longer-lasting skin reactions usually seen after histamine prick. Therefore, we tested brain responses to longer-lasting histamine reaction in healthy participants. Effects of pain due to the prick were controlled by an additional prick condition using saline.

Results

Flare, wheal, and itch Following histamine prick, a substantial local reaction was observed. The mean diameter of flares reached 24 mm and showed a maximum about 5 min after prick. Mean wheal diameters increased continuously up to 6 mm at the end of the session. After saline prick, the flare was considerably smaller and a wheal was never detected. Accordingly, ratings of itch intensity and unpleasantness were much higher after histamine than after the saline prick (see Fig 1).

Brain activation corresponding to itch was found in eight clusters located mainly in frontal regions. Medial frontal activation took place in the superior frontal gyrus and the gyrus rectus in both hemispheres as well as in a small area of the left anterior cingulate gyrus. Right hemispheric clusters were found in the inferior frontal gyrus and in orbital and dorsolateral parts of the superior frontal gyrus. Further activation was located in the left temporal pole and some parts of the left cerebellum (see Table I and Fig 2).

Discussion

In comparison, brain reactivity in connection with tonic itch sensations is much more difficult to investigate in functional magnetic resonance imaging (fMRI) analysis than brain reactivity with regard to pain sensations, where short-term reactions can be evaluated. In this study, we demonstrated the brain activation under the histamine-itch condition in eight different areas of the brain in comparison with saline-placebo control. Brain activation was shown mostly in the superior frontal gyrus, in the temporal pole, in the cerebellum, and the inferior frontal gyrus. No activation differing from the placebo control was found in the postcentral gyrus where activation of body sensations was usually found. The gyrus frontalis medius and gyrus frontalis inferior are known to stimulate the motoric activities of the body, in which sensory input is necessary. In the gyrus frontalis inferior, the secondary sensoric cortex is represented and may be activated during itch reactions. In the cingulate areas emotional components of the itch reaction may exist, because the cingulate cortex is known as being highly correlated to emotions. In the temporal pole medial, there is the inter-

Figure 1

Abbreviation: fMRI, functional magnetic resonance imaging
pretative cortex that represents experiences and remembrance. Perhaps there the present itch is compared with former itch experiences.

But all of these interpretations are still hypothetical with regard to the few studies in this area that looked for activation of the brain. Our results seem to be similar to the finding of McGlone et al (2001), who also showed activation in the forebrain (Brodmann’s area BA10), an area related to perception (Faw, 2003). Further activations that they found in BA21, BA22, and BA40 could not be confirmed by our results. In the PET analyses of previous studies, Darsow et al (2000), Drzezga et al (2001), Hsieh et al (1994), and Mochizuki et al (2003) identified partly different areas of activation in the anterior cingulated cortex, supplementary motor area, premotor area, and inferior parietal lobe. Hsieh et al (1994) demonstrated the coactivation of the anterior cingulate cortex, supplementary motor area, premotor area, and inferior parietal lobule and underpinned the posterior sector of the anterior cingulate cortex as being related to the sensory/affective aspect of the event.

The divergent results may be due to a different method of stimulation with histamine used in this study. We decided to investigate the tonic histamine reaction by prick that produces an itch sensation without producing a substantial pain sensation in a quick and easy way. The PET analyses used in the studies mentioned above have only a very short time frame for revealing activation, whereas fMRI analysis is able to take a longer time period into account. For instance, Darsow et al (2000) described activation for 50 s beginning 2 min after stimulation in the PET analysis. Further studies should evaluate the time course of brain activation during itch.

The “pain matrix” (Derbyshire, 2000; Peyron et al, 2000) also comprises very different regions from those identified in our study. Therefore, we assume that brain processes during itch differ substantially from those during pain. But data based on a small sample like ours cannot be taken as proof for missing activation. Further studies with larger samples are needed to explore the “itch matrix”.

Methods

Subjects Six of eight right-handed healthy non-smoking males (mean age: 25.6 y; ranging from 20 to 30 y) were selected for the study. All of them had no history of allergy, no atopic diseases in

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Table I. Areas of activation (pooled over six subjects) correlated to itch sensation

<table>
<thead>
<tr>
<th>No.</th>
<th>Size</th>
<th>t test</th>
<th>Position</th>
<th>Brain areas (Brodmann areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>7.81</td>
<td>0.000</td>
<td>Superior frontal gyrus, medial orbital, left + right anterior cingulate and paracingulate gyri, left (BA 10)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>7.52</td>
<td>0.000</td>
<td>Superior frontal gyrus, orbital and medial orbital part, left; gyrus rectus, left (BA 10/11)</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>7.46</td>
<td>0.000</td>
<td>Superior frontal gyrus, medial orbital, left gyrus rectus, left + right (BA 11)</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>7.42</td>
<td>0.000</td>
<td>Superior frontal gyrus, orbital and dorsolateral part, right (BA 10)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>6.77</td>
<td>0.000</td>
<td>Temporal pole: middle temporal gyrus, left (BA 38)</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>6.57</td>
<td>0.000</td>
<td>Cerebellum, left, lobule 6, crus 1, 8</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>6.04</td>
<td>0.000</td>
<td>Inferior frontal gyrus, triangular part, right</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>5.44</td>
<td>0.002</td>
<td>Superior frontal gyrus, medial, right (BA 10)</td>
</tr>
</tbody>
</table>

*The numbers correspond to the clusters in Fig 2.
*Number of voxels with p < 0.05 (corrected for entire brain volume); a voxel is a cube of 3 × 3 × 3 mm³.
*Position of the activation peaks in co-ordinates of the MNI (Montreal Neurological Institute digital phantom scan) standard brain.

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Methods

Subjects Six of eight right-handed healthy non-smoking males (mean age: 25.6 y; ranging from 20 to 30 y) were selected for the study. All of them had no history of allergy, no atopic diseases in

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Detailed descriptions of methods are available on request from the authors.
the family, no current diseases, and no current intake of drugs that could influence the study. The remaining two subjects had to be excluded from further analyses because they reported only a slight itch sensation during the experiment (see below). The study was approved by the ethics committee of the medical faculty of the University Giessen, Germany, and performed according to Declaration of Helsinki principles.

**Design** Subjects participated in the fMRI examinations in separate sessions for each of four experimental conditions: subjects received one prick per session with either histamine or saline to the left forearm. The sessions were conducted in partly permuted order with an interval of at least 1 wk. No information about the substance used in the current session was given to the subjects.

**Measures and procedure** After informed consent for the experimental procedure and for the fMRI examination, the participants learned how to use a visual analog scale (VAS) on a standard PC with a keypad. Then, the subjects were placed into the scanner and instructed on how to use the keypad with their right hand. The VAS were presented on a screen that was placed behind the MR scanner and could be observed by means of a mirror. VAS ratings were performed every minute starting 28 s after the onset of the experiment. The ratings could range from zero to hundred. The extremes of the scale for itch intensity were labeled “no itch” (0) and “the most intense itch imaginable” (100). A second VAS was used for the unpleasantness of itch. It was labeled “no itch” (0) and “the most unpleasant itch imaginable” (100) (Yosipovitch, 2003).

The prick was applied 2 min after the start of the experimental session by using plastic needles (Stallergenes, Anthony-Cedex, France). Wheal and flare diameters were taken every 2 min starting 30 s after the prick. The experimental session lasted 17 min.

**Analysis of itch ratings** Subjects who always rated their itch intensity during the histamine condition always lower than 15 were excluded from analyses. This was the case for two subjects. Due to this loss, data only of six subjects are reported here.

**Image acquisition and analysis** fMRI uses the blood-oxygen-level-dependent (BOLD) response (Logothetis and Wandell, 2004), which is basically an increase of oxygenated blood in areas where neural activation takes place. Fast echo-planar imaging sensitive to BOLD signal was applied to acquire every image of almost the whole brain 4 s. A fixed-effect general linear model for the fMRI time series at each volume element (voxel) was used in order to compare activation between the two conditions (histamine vs saline prick). The mean time course of itch sensation reported by the six subjects during the histamine sessions served as a regressor for both sessions. The comparison of regression coefficients obtained in histamine and saline sessions gives the activation correlated with itch intensity pooled over subjects. The rating procedure, the prick itself, and head motion parameters were considered as additional covariates for controlling their possibly confounding effects. The significance level was set to α = 0.05 after controlling for multiple comparisons due to the analysis of the whole brain volume using the random field theory.

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**References**


