Neural basis of contagious itch and why some people are more prone to it

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Watching someone scratch himself can induce feelings of itchiness in the perceiver. This provides a unique opportunity to characterize the neural basis of subjective experiences of itch, independent of changes in peripheral inputs. In this study, we first established that the social contagion of itch is essentially a normative response (experienced by most people), and that the degree of contagion is related to trait differences in neuroticism (i.e., the tendency to experience negative emotions), but not to empathy. Watching video clips of someone scratching (relative to control videos of tapping) activated, as indicated by functional neuroimaging, many of the neural regions linked to the physical perception of itch, including anterior insular, primary somatosensory, and prefrontal (BA44) and premotor cortices. Moreover, activity in the left BA44, BA6, and primary somatosensory cortex was correlated with subjective ratings of itchiness, and the responsivity of the left BA44 reflected individual differences in neuroticism. Our findings highlight the central neural generation of the subjective experience of somatosensory perception in the absence of somatosensory stimulation. We speculate that the habitual activation of this central “itch matrix” may give rise to psychogenic itch disorders.

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(n = 18) completed the task during fMRI scanning (providing both behavioral and neuroimaging data); however, this group was explicitly instructed to refrain from scratching while in the scanner.

Results
Behavioral Results: Itch Ratings. A repeated-measures ANOVA on the rating data with the factors Condition (scratch vs. control), Sex of person shown in the video) and Body Part (five locations) was conducted. The results are summarized in Fig. 1. There was a significant main effect of Condition \( [F(1,50) = 56.45; P < 0.001] \). That is, the video clips depicting scratching elicited greater feelings of itchiness than the control videos, and the effect size was large (Cohen’s \( d = 0.85 \)). In addition, there was a main effect of Body Part \( [F(4,200) = 2.77; P < 0.05, \text{Greenhouse–Geisser corrected}] \), with post hoc \( t \) tests confirming that scratching of the left upper arm site elicited greater itchiness than the other sites that did not differ from one another (a small effect size of \( d = 0.14 \) comparing the left upper arm with the mean of other sites). No other main effects or interactions were significant. The itch ratings on trial N were uncorrelated to the ratings on trial \( N + 1 \), suggesting that induced itchiness did not carry over significantly from trial to trial (mean correlation, \( 0.05 \pm 0.24 \)). As such, we confirmed that the stimuli are appropriate inducers of itch, and, moreover, that experiencing itch from observing itch is essentially a normative response. However, the magnitude of this response differed across individuals; for example, the range of mean scores in response to the scratching videos was \( 0.00–6.03 \).

To further verify the validity of our approach, we identified and counted occurrences of spontaneous rubbing or scratching movements made by participants during the behavioral experiment by analyzing the video recordings. Overall, 64% of participants (21 of 33) produced at least one such movement during the experiment (mean, 6.7 movements). A total of 132 scratches (59.5%) were produced during or immediately after observing a scratch video, compared with 90 scratches (40.5%) for the control condition. There was a significant association between the type of video watched and whether or not participants would scratch themselves \( [\chi^2(1) = 11.09; P < 0.001] \). This seems to reflect the fact that, based on the odds ratio, the odds of participants scratching themselves were 1.64-fold greater if they were currently watching a scratch video compared with watching a control video.

Behavioral Results: Individual Differences in Itch Contagion. Itch contagion was calculated as the tendency to report itchiness in response to videos of scratching relative to the control stimuli (difference score; scratch − control ratings). We first established that participant sex does not significantly affect itch contagion. There was no difference in level of itch contagion between male and female participants [difference scores of \( 1.02 \pm 1.33 \) and \( 1.53 \pm 1.33 \), respectively; \( t(49) = 1.27; \text{both } P = \text{not significant} \)]. We then correlated the difference scores with the various scales on the personality and empathy questionnaires (24–26). In terms of correlations with trait variables, the sole significant predictor was neuroticism, the tendency to experience negative emotions \( (r = 0.34; P < 0.05) \). Higher neuroticism was linked to greater itch contagion. The full pattern of correlations is summarized in Fig. S1. Of note, there was no tendency to link empathy and itch contagion, with many of the empathy scales showing negative trends in such areas as “perspective taking” (the tendency to take someone else’s viewpoint) and “empathic concern” (the tendency to respond compassionately).

Finally, we found that the intensity of itch ratings was linked to the number of spontaneous scratches produced during the experiment \( (r = 0.35; P < 0.05) \). In other words, participants who assigned higher overall itch ratings in response to the video stimuli also tended to scratch themselves more often while watching these videos.

fMRI Results. We found that observing scratching movements relative to observing control (tapping) movements activated the major areas of the itch matrix, including the thalamus, primary somatosensory cortex, premotor cortex (BA6), and insula. We also noted activation in the left BA44, extending into BA6, as well as bilateral activations in the lateral-occipital complex and cerebellum (Fig. 2 A and Table 1). The reverse contrast (tapping-scratch) revealed no significant activations. We next used the itchiness ratings that participants assigned after each video to characterize the degree to which responses within the activated brain regions correlated with the subjective experience of itch. This parametric analysis indicated that only activity in the left BA44, primary somatosensory cortex, and BA6 was significantly related to itch intensity \( (r = 0.69, 0.90, \text{and 0.71, respectively; Fig. 2 B}) \). The correlation did not meet the criterion for significance in the right insula \( [r(13) = 0.47; P = 0.067] \). Results for the whole-brain analysis of the parametric itch effect are shown in Fig. S2.

Given the behavioral finding of an association between neuroticism and itch contagion, we entered the individual factor score for this particular trait as a covariate into the group-level statistical model. This allowed us to identify brain areas in which the magnitude of the brain-based categorical itch effect (scratch − control) was significantly correlated with neuroticism. Left BA44 was the only region to show a significant correlation, and the direction of the correlation was positive (Fig. 2 D).

To further characterize how activation levels change over the course of the 20-s clips, we assessed the strength of the categorical itch effect (scratch − control) separately for the first half (1–10 s) and the second half (11–20 s) of each block. This analysis revealed left BA2, BA44, and BA6 activation only during the first 10 s of a video, suggesting a more stimulus-driven role for these areas. In contrast, activation in the right anterior insula was much more sustained, suggesting a more continuous process occurring in this area.

Discussion
The first important finding of the present study is that on a behavioral level, social contagion of itch is a normative response (i.e., experienced by most people). When participants were free to scratch, most (64%) did so at least once. This puts itch on a par with other types of socially contagious behavior, including laughter (47%; ref. 27) and yawning (40–60%; refs. 21, 28). Furthermore, participants who experienced stronger feelings of itchiness during the experiment also tended to spontaneously scratch themselves more often when free to do so, indicating a correspondence between self-report and observable behavior.
Our findings characterize the central neural substrates mediating the social contagion of itch by identifying regions that support the subjective experience of itch. Importantly, observing itch activated the same set of brain regions associated with feelings of itch induced by an irritant, such as histamine (5–7). This shared network includes the anterior insula, premotor cortex, primary somatosensory cortex, and prefrontal cortex. One region not activated in our study but typically activated by chemical induction of itch is the midcingulate cortex, although not all studies of itch have reported activity here (14, 29). The magnitude of activation across this “itch matrix” reflects the main effect of viewing itch-related videos (relative to non-itch control stimuli), and tends to correlate with the subjective intensity of itchiness reported for these stimuli.

There is good evidence that the anterior insula is a core node in the network for shared pain (reviewed in ref. 23), and our results demonstrate that itch may be shared in the anterior insula as well. Furthermore, the response in the right anterior insula was sustained throughout the duration of the stimulus, in contrast to most other regions, which displayed a strong response in the early phase only (Fig. 2C). The (right) anterior insula is part of a tightly connected neural network engaged in interoceptive awareness (30), that is, representation of motivationally salient subjective feelings related to the body’s internal state, including C-fiber–mediated sensations such as itch, tickle, and visceral pain (31). These insular bodily representations may subserve at least two functions relevant to contagious itch. First, the anterior insula may act as a comparator in a predictive coding model of interoception, according to which subjective feeling states arise from top-down predictions of interoceptive signals (32). Second, these predictive representations may allow simulation of how a specific stimulus feels to others (33). Combining these views,
The participants included 51 healthy volunteers. Eighteen par-
models (male, female). The study was approved by the Research Governance and Ethics Committee of the Brighton and Sussex Medical School. Participants received financial compensation at a rate of £5/h.

Finally, some patients report persistent itch sensations (often accompanied by a belief of infestation) but appear dermatologically normal (45). It is likely that the same central mechanisms responsible for itch sensations induced by observing itch in others (an essentially normative response) is responsible for itch induced by self-generated thoughts of itching or infestation (which may become established as dominant overvalued representations in a minority of persons). Individual differences within this network, also related to personality traits, may modulate the extent to which this contagion is triggered by environmental cues versus occurring spontaneously and habitually (46, 47). Further research is warranted to explore the link between contagious itching and compulsive itching.

Methods
Participants. The participants included 51 healthy volunteers. Eighteen participants took part in the fMRI procedure (9 males, 9 females; mean age, 20.9 y; range, 18–29 y), and the remainder completed the behavioral ratings and questionnaires outside of the scanner (8 males, 25 females; mean age, 21.2 y; range, 18–35 y). All participants provided written informed consent. The study was approved by the Research Governance and Ethics Committee of the Brighton and Sussex Medical School. Participants received financial compensation at a rate of £5/h.

Stimulus Materials. Short (20-s) video clips were created in advance for this experiment, showing either body scratching or a control movement. Scratching consisted of continuous scraping of the target site using four curled fingers of one hand. Five different target sites were used: left forearm, left upper arm, chest, right forearm, and right upper arm. The control videos showed continuous tapping of a target site. Two different models were filmed (one male, one female) from the waist up to the neck, ensuring that the head was never visible. The total stimulus set comprised 20 videos [2 conditions (scratch vs. control) × 5 target sites × 2 models (male, female)].

Procedure. The same basic procedure was used for all participants. However, participants completing the task in the scanner underwent four experimental runs (instead of two) to maximize the number of brain volumes acquired. Those tested outside the scanner completed the study seated at a computer screen in a testing room. They were also filmed during the experiment.

Participants tested in the scanner were placed in a supine position, and visual stimuli were projected on a screen behind the scanner, which the participant could view via a mirror mounted in the head coil. The experiment had a blocked fMRI design. At the beginning of each block, one video (lasting 20 s) was shown, followed by the acquisition of one brain volume [repetition time (TR) of 3.3 s] during which a fixation cross was displayed. Next, the participant was asked to rate the intensity of itchiness (if any) induced by the

Table 1. Regions showing significant activation in the contrast of scratch vs. control

<table>
<thead>
<tr>
<th>Anatomic region</th>
<th>k</th>
<th>z-score</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior parietal cortex (40% BA2*, 40% hIP3)</td>
<td>682</td>
<td>5.38</td>
<td>−33</td>
<td>−43</td>
<td>52</td>
</tr>
<tr>
<td>Left superior parietal lobe (80% 7A*)</td>
<td>4.57</td>
<td>−18</td>
<td>−58</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Left inferior parietal cortex (60% PIt*, 50% BA2)</td>
<td>4.25</td>
<td>−54</td>
<td>−25</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA44, extending into BA6)</td>
<td>43</td>
<td>3.76</td>
<td>54</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Left superior frontal gyrus (20% BA6)</td>
<td>108</td>
<td>4.34</td>
<td>−24</td>
<td>−10</td>
<td>55</td>
</tr>
<tr>
<td>Left precentral gyrus (50% BA6)</td>
<td>3.78</td>
<td>−24</td>
<td>−16</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Left superior frontal gyrus</td>
<td>3.16</td>
<td>−24</td>
<td>−1</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Left insula</td>
<td>27</td>
<td>3.72</td>
<td>−42</td>
<td>−4</td>
<td></td>
</tr>
<tr>
<td>Right insula (anterior)</td>
<td>49</td>
<td>3.98</td>
<td>45</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>3.61</td>
<td>45</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Ventral aspect of thalamus</td>
<td>27</td>
<td>3.97</td>
<td>−3</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>Left middle occipital gyrus (40% hOCS V5/MT*)</td>
<td>134</td>
<td>4.67</td>
<td>−45</td>
<td>−76</td>
<td></td>
</tr>
<tr>
<td>Right middle occipital gyrus</td>
<td>89</td>
<td>3.92</td>
<td>45</td>
<td>−73</td>
<td></td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>25</td>
<td>3.89</td>
<td>−9</td>
<td>−34</td>
<td></td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>24</td>
<td>3.93</td>
<td>21</td>
<td>−70</td>
<td></td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>49</td>
<td>3.86</td>
<td>24</td>
<td>−61</td>
<td></td>
</tr>
</tbody>
</table>

The most probable anatomic region in the Anatomy Toolbox 1.8 (28) is in parentheses. k, cluster size in voxels; x, y, and z, MNI coordinates.

*Indicates assigned regions.
preceding video. The participant recorded his or her rating via button press on a scale of 0 (not at all) to 7 (extremely), with 4 indicating moderate itch. The display included a visual estimation of the response remaining on the screen for each TR (3.3 s), followed by another 3 TRs during which a fixation cross was shown. One experimental run consisted of 20 blocks and lasted approximately 12 min. It was essential that the participant remain still during the scanning session and refrain from scratching during experimental runs. (No such instructions were given in the behavioral part of the study.) Each participant was observed by the experimenter to ensure compliance. The participants also completed several questionnaires, including the Big Five Inventory (BFI) (25), the Empathy Quotient (EQ) (26), and the Interpersonal Reactivity Index (IRI) (24). One participant failed to complete the IRI, and the EQ was introduced only after the first 23 participants had been tested.

**Imaging Data Acquisition.** To minimize signal artifacts originating from the sinuses, axial slices were tilted 30° from the intercommissural plane. Thirty-six slices (3 mm thick, 0.75 mm interslice gap) were acquired on a 1.5-T Siemens Avanto magnetic resonance scanner with an in-plane resolution of 3 × 3 mm (repetition time = 3.3 s per volume, echo time = 50 ms).

**Imaging Data Analysis.** FMRI data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) and Matlab R2007b (MathWorks). Standard spatial preprocessing [realignment, coregistration, segmentation, normalization to Montreal Neurological Institute space, and smoothing with an 8-mm FWHM Gaussian kernel] was performed. Voxel size was interpolated during preprocessing to isotropic 3 × 3 × 3 mm.

Two statistical models, a categorical model and a parametric model, were calculated for each participant. For the categorical analysis, the two experimental conditions (scraping and control) were modeled separately as stimulation blocks time-locked to the entire duration of each video (20 s each). Six movement regressors were also included to regress out any residual variance from head movement.

The parametric model included three regressors: a boxcar regressor covering the duration of each video presentation (scratch and control), and a regressor modeling the parametric modulation of these periods by the linear effect of itchiness (as indicated by the rating obtained after each video), and a regressor modeling the quadratic effect of itchiness (to allow for curvilinear relationships). Three participants had at least one run in which no variation in rating response occurred (all zero ratings, meaning that no itch was induced by any of the stimuli). These three participants were excluded from the parametric analysis, because it was not possible to estimate a statistical model in these cases.

Statistical parametric maps of contrast estimates of experimental effects from individual participant analyses were entered into second-level group analyses performed using SPM8. To protect against false-positive results, a double threshold was applied in which only regions with a z-score exceeding 3.09 (P < 0.001, uncorrected) and a volume exceeding 378 mm³ were considered. Thresholds were determined in a Monte Carlo simulation using a Matlab script provided by Scott Slotnick (https://www2.bc.edu/ed-slotnick/scripts.htm). This approach provided a statistical correction for multiple comparisons corresponding to P < 0.05, corrected.

To ensure that the parametric analysis and all reported correlations were unbiased (48, 49), different data were used for selecting the regions of interest (run 4) and computing the correlations (runs 1–3). Regions of interest were created using the MarsBar toolbox.

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