

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.

functional MRI | pruritus | visual induction | insula | touch

Itch is—to some degree—socially contagious. Subjective feelings of itchiness and observable increases in scratching can be evoked by watching someone scratch himself or by listening to a lecture on dermatologic conditions (1, 2). Although many aspects of the neurobiology of itch are now appreciated (3, 4), the standard definition of itch (“an unpleasant sensation associated with an urge to scratch”) and its description as a symptom within clinical disorders remain essentially subjective and based on self-report. The study of the neural basis of contagious itch presents a unique opportunity to explore the neural basis of subjective itch experience that is dissociated from the normal peripheral inputs.

Functional neuroimaging investigations of itch [predominantly functional MRI (fMRI)] typically use an invasive, localized administration of histamine to induce itch (5–8). This approach has revealed the engagement of a network of regions (the so-called “itch matrix”) that includes the anterior insula, cingulate cortex, primary somatosensory cortex, premotor cortex, prefrontal cortex, thalamus, and cerebellum. Within this network, there is functional specialization that reflects the multifaceted nature of itch (i.e., its sensory, motor, and affective attributes), with the proposal that anterior insula and cingulate cortex may code the affective components of itch (4). Of note, these regions are also linked to the processing of (and awareness of) interoceptive bodily signals, including pain, cardiovascular activity, and hunger (9, 10). These internal signals are motivationally salient, and thus their representation may correspondingly engender an urge for action (11)—that is, scratching in the case of itch. The planning of scratching movements is linked to premotor activity, whereas the intention to scratch (or not) is linked to engagement of the prefrontal cortex (12), consistent with this area’s recognized role in willed actions (13). Primary and secondary somatosensory

cortices have been proposed to support the sensory (i.e., spatial, temporal, and intensity) aspects of the experience (4); however, activity within almost all parts of the itch matrix is correlated with subjective ratings of itch intensity (5, 6, 14), suggesting interdependence of the sensory, motor, and affective components of itch. Previous fMRI studies were constrained by the methodological limitation that the experience of histamine-induced itch emerges rather slowly, taking approximately 1 min to reach peak intensity after onset of infusion (5), followed by a slow decay. This time course means that little of the moment-to-moment fluctuation in subjective itchiness can be related to evoked changes in brain activity, constraining analytic power. We show that visual induction of itch does not suffer from this limitation.

Although no previous study has examined the neural correlates of visually induced itch, several researchers have suggested that the “mirror neuron system” may be essential for contagious itching (2, 4). Mirror neurons, first reported in the macaque brain, respond to both a self-executed action and the sight of an action performed by another person (15). In macaques, mirror neuron-containing regions include the premotor and inferior frontal cortices and inferior parietal lobe (16). Neurons with similar properties have been observed in the human brain as well (17). In humans, this system may extend beyond action perception to perception of feeling states. For instance, Carr et al. (18) suggested that viewing a facial expression activates emotion-related parts of the brain via the motor-based mirror system, and that this could be the neural basis of empathy (19). There is compelling evidence linking empathy with some forms of emotional or behavioral “contagion” (20, 21), although contagious itch has not been considered in any previous studies. However, some studies did not implicate action-based mirror systems as the interface between perception and feeling (22, 23), but suggested instead that feeling states can be shared without obligatory motor simulation.

In the present study, we used fMRI to examine the neural basis of contagious itch. Before conducting the neuroimaging study, it was important to verify that itch sensations could be reliably induced from the visual observation of scratching actions (Fig. 1). In this behavioral study, video clips showing images of one of two people (male, female) scratching one of five body parts (upper/lower × left/right arm, and midline chest) were shown to participants. Still images from these videos are shown in Fig. 2. An equal number of control videos showed people tapping the same body part. After each video was viewed, the participants ($n = 33$) were asked to rate how itchy they felt on a scale of 0 to 7. Participants were filmed during the behavioral study, allowing analysis of the degree to which observing the stimuli elicited spontaneous scratching. Another group of participants

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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 [$F(4,200) = 2.77$; $P < 0.05$, 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 ± 0.24). As such, we confirmed that the stimuli are appropriate inducers of itch, and, moreover, that experiencing itch from observing it 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

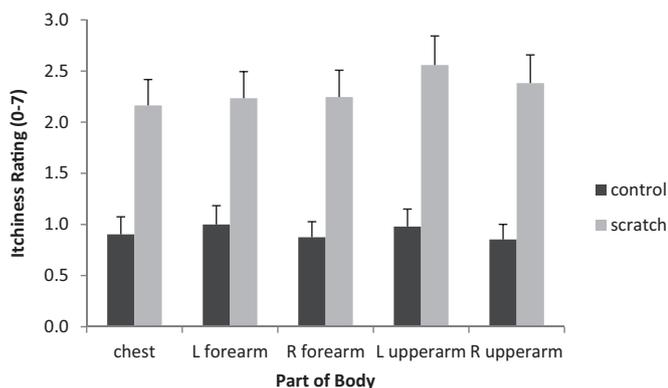


Fig. 1. Degree to which watching videos induced feelings of itchiness in the participants, as indicated by ratings. The scale ranges from 0 (not at all) to 7 (extremely), with 4 as moderate. $n = 51$. Error bars indicate 1 SEM.

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 ± 1.33 and 1.53 ± 1.33 , respectively; $t(49) = 1.27$; both P s = 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 toward a link between 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. 2A 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 ($r = 0.69, 0.90$, and 0.71 , respectively; Fig. 2B). 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. 2A).

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.

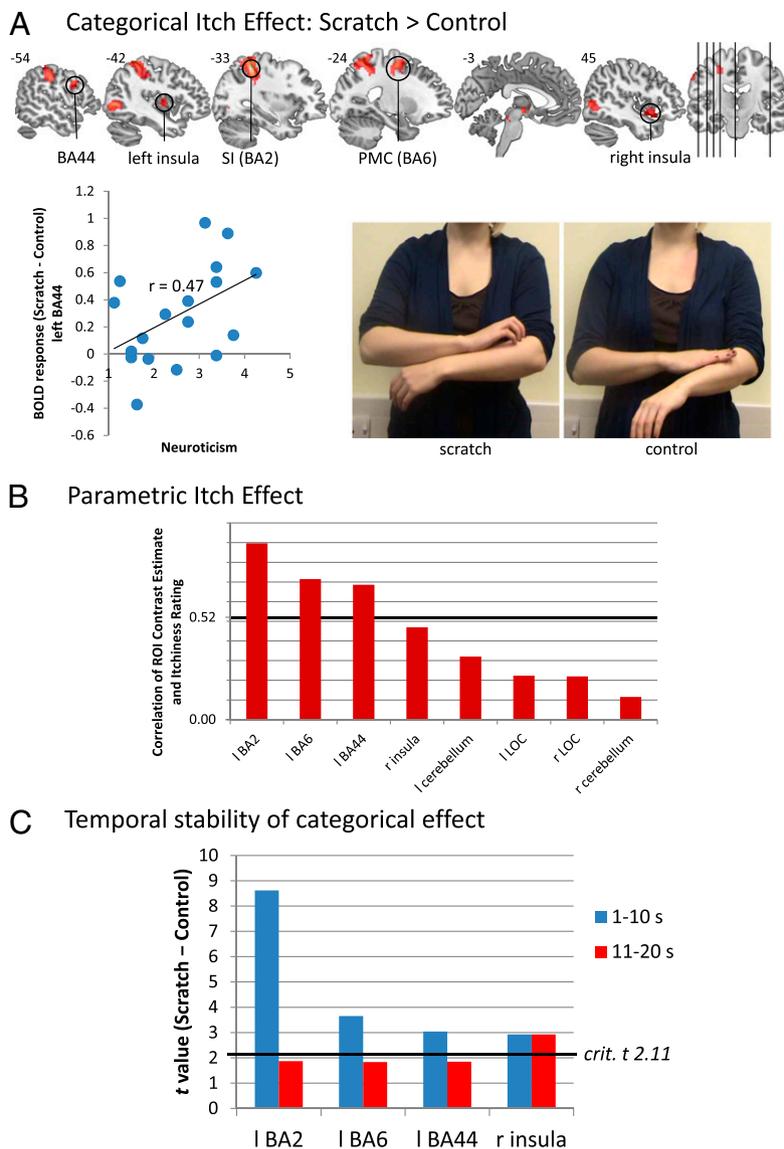


Fig. 2. (A) Cross-sections showing regions significantly activated ($P < 0.05$, corrected) in the comparison of scratch and control. $n = 18$. The position of sagittal slices is indicated by the number above (x coordinate in the MNI system) and is also shown in the coronal section on the right. The scattergram shows a significant correlation between the magnitude of the categorical itch effect in left BA44 and neuroticism, as measured by the BFI (50). (B) Magnitude of the parametric itch effect in key regions. $n = 15$. The bold black line indicates the significance threshold (all $r > 0.52$ are significant at $P < 0.05$, two-tailed). LOC, lateral occipital complex. (C) t values of the categorical effect in key regions for the first half (1–10 s) and second half (11–20 s) of the 20-s video clips. $n = 18$. The critical t value ($P < 0.05$, two-tailed) is in bold black.

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,

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

Anatomic region	k	z-score	x	y	z
Left inferior parietal cortex (40% BA2*, 40% hIP3)	682	5.38	-33	-43	52
Left superior parietal lobule (80% 7A*)		4.57	-18	-58	64
Left inferior parietal cortex (60% Pft*, 50% BA2)		4.25	-54	-25	40
Left inferior frontal gyrus (BA44, extending into BA6)	43	3.76	-54	8	31
Left superior frontal gyrus (20% BA6)	108	4.34	-24	-10	55
Left precentral gyrus (50% BA6)		3.78	-24	-16	49
Left superior frontal gyrus		3.16	-24	-1	46
Left insula	27	3.72	-42	-4	4
Right insula (anterior)	49	3.98	45	14	-11
Right insula		3.61	45	5	-8
Ventral aspect of thalamus	27	3.97	-3	-10	-5
Left middle occipital gyrus (40% hOC5 V5/MT*)	134	4.67	-45	-76	1
Right middle occipital gyrus	89	3.92	45	-73	4
Left cerebellum	25	3.89	-9	-34	-17
Right cerebellum	24	3.93	21	-70	-23
Right cerebellum	49	3.86	24	-61	-41

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.

anterior insula activity thus may be related to sharing the unpleasant bodily sensations that accompany itch.

Several of the brain regions linked to contagious itch are implicated in the simulation of actions (mirror systems), including the premotor cortex (BA6) and adjacent BA44 (34, 35). The primary somatosensory cortex (BA2) is also commonly activated during action observation (34), but also plausibly could code the sensory aspects of itch. In all three of these regions, activity was greatest in the earlier half of the stimulus presentation. This is more consistent with involvement of these regions in the perception of itch than in, say, the generation of scratching urges. The latter would be expected to build up over the duration of the stimulus (although we did not explicitly measure how the subjective experience unfolds over time). However, each of these regions likely has a relatively different functional contribution that remains to be fully elucidated. The area of activity in primary somatosensory cortex lies in the left hemisphere hand area (36), suggesting that it may code the sensory effects of scratching (rather than the location being scratched). Along with a role in the simulation of actions, the premotor cortex also responds to somatosensory stimuli (37–39) and the sight of touch (40–42); thus, in principle, its role also may be sensory-based rather than action-based. However, premotor and somatosensory cortices differ in the degree to which they are also activated by the control condition of tapping. The premotor region does not respond to this control action relative to fixation, whereas somatosensory cortex does respond (Fig. S3). This could reflect different motoric demands that affect primarily the premotor cortex; for example, scratching requires complex manipulation of fingers, but tapping is a far simpler wrist-based action.

Itch-related activity in the left BA44 is correlated with neuroticism, and neuroticism itself has been identified as the sole reliable trait predictor of individual differences in subjective feelings of itch contagion. This trait is known to exacerbate certain clinical symptoms, such as chronic pain (43), and is a predisposing influence in various psychopathologies (44). The importance of neuroticism as social processing of empathy might reflect a key difference between the social processing of itch versus pain that may originate in distinct motivational biases toward social proximity (pain) or distance (itch). The prefrontal cortex is generally implicated in the control of cognition and behavior, and in the present context it may serve a gating (attention-related) function that modulates the degree of contagion.

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

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 itchiness. The display prompting a response remained on the screen for one 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 (MNI) 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 (scratch and control) were modeled separately as stimulus 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), 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 a least one run in which no variation in rating response occurred (all zero ratings, meaning that no itch was induced by any of the visual 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/sd-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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