



# The functional and structural alterations of the striatum in chronic spontaneous urticaria

## Citation

Wang, Y., J. Fang, B. Cui, J. Liu, P. Song, C. Lang, Y. Bao, et al. 2018. "The functional and structural alterations of the striatum in chronic spontaneous urticaria." *Scientific Reports* 8 (1): 1725. doi:10.1038/s41598-018-19962-2. <http://dx.doi.org/10.1038/s41598-018-19962-2>.

## Published Version

doi:10.1038/s41598-018-19962-2

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:35014942>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

# SCIENTIFIC REPORTS



OPEN

## The functional and structural alterations of the striatum in chronic spontaneous urticaria

Yuming Wang<sup>1,2</sup>, Ji-Liang Fang<sup>4</sup>, Bingnan Cui<sup>1</sup>, Jiao Liu<sup>2,3</sup>, Ping Song<sup>1</sup>, Courtney Lang<sup>2</sup>, Yan Bao<sup>4</sup>, Ruirui Sun<sup>2</sup>, Chenchen Xu<sup>1</sup>, Xu Ding<sup>1</sup>, Zhifang Yan<sup>1</sup>, Yuhe Yan<sup>1</sup>, Qian Kong<sup>1</sup> & Jian Kong<sup>2</sup>

The brain has long been known to be the regulation center of itch, but the neuropathology of chronic itch, such as chronic spontaneous urticaria (CSU), remains unclear. Thus, we aimed to explore the brain areas involved in the pathophysiology of CSU in hopes that our results may provide valuable insights into the treatment of chronic itch conditions. 40 CSU patients and 40 healthy controls (HCs) were recruited. Urticaria activity scores 7 (UAS7) were collected to evaluate patient's clinical symptoms. Amplitude of low frequency fluctuations (ALFF), voxel-based morphometry (VBM), and seed-based resting-state functional connectivity (rs-FC) analysis were used to assess brain activity and related plasticity. Compared with HCs, CSU patients exhibited 1) higher ALFF values in the right ventral striatum / putamen, which were positively associated with clinical symptoms as measured by UAS7; 2) gray matter volume (GMV) increase in the right ventral striatum and putamen; and 3) decreased rs-FC between the right ventral striatum and the right occipital cortex and between the right putamen and the left precentral gyrus. Using multiple-modality brain imaging tools, we demonstrated the dysfunction of the striatum in CSU. Our results may provide valuable insights into the neuropathology and development of chronic itch.

Chronic spontaneous urticaria (CSU) is a common disorder characterized by the spontaneous eruption of short-lived (<24 h) itchy wheals, with or without angioedema, for a period longer than 6 weeks<sup>1</sup>. CSU affects 0.5–1.0% of the population at any given time and severely diminishes the quality of life of patients<sup>2,3</sup>. Despite its prevalence, there is a lack of understanding of the pathology of CSU and consequently, limited treatment options. Standard therapy with regular doses of non-sedating second-generation H1 antihistamines (H1AH) are ineffective for more than 50% of patients with CSU<sup>2</sup>.

Accumulating evidence suggests that the skin and brain are functionally connected<sup>4,5</sup>. For instance, the brain shares numerous mediators with skin through the hypothalamic-pituitary-adrenal axis (HPA axis)<sup>4</sup>. Studies have shown that the HPA axis may be altered in stress-related skin diseases, resulting in the activation of mast cells<sup>6,7</sup>, which are the primary effector cells in CSU<sup>8</sup>.

The most common clinical manifestation of CSU is repeated itching and scratching. Studies suggest that the brain plays a key role in the itch-scratch cycle<sup>9</sup>. Functional brain imaging studies have identified brain regions associated with the itch-scratch cycle, such as the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), primary motor cortex (MI), premotor cortex (PM), supplementary motor area (SMA), cerebellum, the prefrontal cortex (PFC), the striatum, and thalamus<sup>10–14</sup>.

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has been applied to investigate the intrinsic functional organization of the brain<sup>15–17</sup>. There are many resting-state fMRI data analysis methods, some of which focus on local connectivity and examine the properties of spontaneous local brain activity, such as the amplitude of low-frequency fluctuations (ALFF), and others which focus on long-range connectivity among different brain regions, such as seed-based resting state functional connectivity<sup>18</sup>. As a reliable and reproducible

<sup>1</sup>Department of Dermatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. <sup>2</sup>Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA 02129, USA. <sup>3</sup>National-Local Joint Engineering Research Center of Rehabilitation Medicine Technology, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian 350122, China. <sup>4</sup>Department of Radiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. Yuming Wang, Jiliang Fang, Bingnan Cui and Jiao Liu contributed equally to this work. Correspondence and requests for materials should be addressed to Y.W. (email: [wangyumingmmm@163.com](mailto:wangyumingmmm@163.com)) or J.K. (email: [kongj@nmr.mgh.harvard.edu](mailto:kongj@nmr.mgh.harvard.edu))

	HC (n = 40)	CSU group (n = 40)
Gender (male/female)	8/32	8/32
Age (year)	42.6 ± 10.8	42.6 ± 10.8
UAS7	—	30.8 ± 6.2

**Table 1.** Demographic and clinical characteristics between HCs and CSU group. Values are presented as mean ± SD.

data-driven method, ALFF can measure the total power of a given time course within a typical frequency range (e.g., 0.01–0.08 Hz), which has been proven to be a valuable index of regional spontaneous neuronal activity<sup>19,20</sup>. Disruptions in ALFF have been observed in several disorders such as chronic pain<sup>21–24</sup>. In addition to brain function changes, previous studies have also found brain structure changes in patients with chronic itch. For instance, Papoiu *et al.* found gray matter density was significantly increased in the brain stem, hippocampus, amygdala, ventral striatum, and putamen in chronic itch patients with end-stage renal disease<sup>25</sup>.

In the present study, we combined local and long-range resting-state methods with voxel-based morphometry (VBM) analysis to explore the differences in resting state brain activity and brain structure between CSU patients and matched healthy controls (HCs). Many CSU patients suffer from itchy wheals, which generally occur at a specific and consistent time every day, usually during the evening or early morning<sup>26</sup>. To avoid itching intensity variation as a confound, all scans were applied while the CSU patients did not have any itching sensations. We hypothesized that CSU patients would have disrupted brain activity and related plasticity of the brain reward pathways, especially in the striatum.

## Results

**Demographic characteristics.** Forty CSU patients (32 female and 8 male) completed the fMRI scan. Forty healthy individuals were matched by age and gender (Table 1).

**ALFF results.** Compared with healthy controls, CSU patients showed significant ALFF increases at the right striatum, including the ventral striatum and putamen (Fig. 1A; Table 2). No other significant regions were identified.

To further test the association between the ALFF values of the observed cluster and UAS7, we extracted the ALFF values (n = 40) from the right striatum cluster and performed a correlation analysis for CSU patients. The results showed that the ALFF values were positively associated with UAS7 ( $r = 0.352$ ,  $p = 0.026$ ) (Fig. 1B).

**VBM results.** Significant gray matter volume (GMV) increases were found in the CSU group compared to the healthy control group in the right putamen (cluster size 90, MNI peak coordinates: 30; 14; 6) and right ventral striatum (cluster size 222, MNI peak coordinates: 14; 6; -4) (Fig. 1C).

**rs-FC results.** To further investigate the network associated with the striatum, we used the right ventral striatum and putamen, which were identified by VBM analysis, as ROIs and performed a seed-based resting state functional connectivity (rs-FC) analysis.

We found that CSU patients demonstrated decreased rs-FC between the right ventral striatum and right occipital cortex and between the right putamen and left precentral gyrus (Table 3). There were no significant increases observed at the threshold we set.

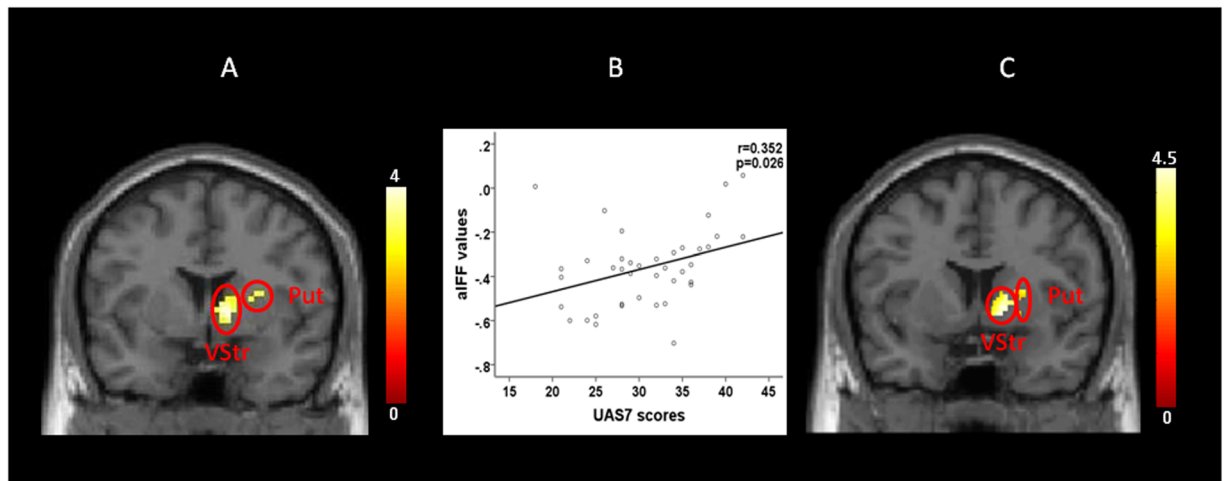
## Discussion

In this study, we investigated ALFF differences, gray matter volume, and seed based rs-FC between CSU patients and healthy controls. We found that CSU patients exhibited higher ALFF values in the right ventral striatum and putamen. These ALFF values were positively associated with clinical symptoms as measured by UAS7. In addition, significant gray matter volume (GMV) increases were found in the CSU group compared to the healthy group in the right putamen and ventral striatum. Furthermore, seed-based rs-FC analysis showed decreased rs-FC between the right ventral striatum and right occipital cortex and between the right putamen and left precentral gyrus. These findings may provide valuable insights into the neuropathology of chronic itch conditions.

The striatum is one of the nuclei in the subcortical basal ganglia and receives glutamatergic and dopaminergic inputs from different brain regions, as well as serving as the primary input to the rest of the basal ganglia nuclei<sup>27</sup>. It is composed of three nuclei: caudate, putamen, and ventral striatum, and each is associated with different functions, including reward, motivation, reinforcement and motor- and action-planning<sup>28</sup>.

In this study, we found increased ALFF and gray matter volume at the ventral striatum in CSU patients compared with HCs. The ventral striatum plays an important role in processing rewarding stimuli, reinforcing stimuli (e.g., food and water), and stimuli which are both rewarding and reinforcing (addictive drugs, sex, exercise and placebo response)<sup>29,30</sup>. Previous studies suggest that the ventral striatum is involved in the relief of itch by scratching<sup>31</sup> and is selectively activated during emotional stimulation<sup>32,33</sup>. The most common clinical manifestation of CSU is repeated itchy wheals and scratching. Scratching an itch, a pleasurable experience, is correlated with the intensity of the itch<sup>34,35</sup>. This pleasurable experience is associated with reward regions<sup>36,37</sup>, which are activated by itch even when there is no scratching behavior<sup>38,39</sup>. Molecular mapping also showed an increased number of c-Fos neurons in the ventral striatum and putamen of mice that displayed contagious scratching<sup>40</sup>.

The putamen is a key region within the basal ganglia-thalamic circuit and is involved in action motivation and initiation, as well as in habitual and repetitive behaviors<sup>41,42</sup>. Previous studies have found that the putamen is



**Figure 1.** (A) Significant differences of ALFF values in right ventral striatum/putamen between the CSU and HCs (CSU > HCs). (B) The ALFF values of this cluster in the CSU group were positively correlated with the UAS7 scores ( $r = 0.352$ ,  $p = 0.026$ ). (C) Increased gray matter volume in CSU compared with HCs in right ventral striatum (VStr) and putamen (Put).

contrast	Brain Regions	MINI coordinates			Peak Z-value	Number of Voxels in the cluster
		X	Y	Z		
CSU > HC	right ventral striatum	12	3	0	3.88	130
	right putamen	24	12	-6	3.46	
HC > CSU	None-					

**Table 2.** Brain regions with significant differences in ALFF values among CSU and HCs.

seed	contrast	Brain regions	Cluster size (voxels)	Peak z-score	MNI coordinates		
					X	Y	Z
right ventral striatum	HCs > CSU	Right occipital cortex	463	4.28	40	-68	20
	CSU > HCs	None-	—	—	—	—	—
right putamen	HCs > CSU	Left precentral gyrus	270	3.97	-36	-12	66
	CSU > HCs	None-					

**Table 3.** Brain regions showing significant functional connectivity differences with the seed.

closely related to the processing of the itch-scratch cycle. Significant activation of the putamen was found during the scratch process of patients with chronic itch<sup>43</sup> and when an itch was produced by mediators (e.g. cowhage)<sup>44</sup>.

Interestingly, the activity of the putamen during an itch before scratching suggests that this brain region may also code the urge to scratch<sup>43,45</sup>. The putamen can be activated by sedating antihistamines, which may relieve itch by instigating patterns of brain activity similar to those induced by scratching an itch<sup>46</sup>. Thus, the ventral striatum and putamen seems to play an important role in the suppression of itch by the regulation of scratch.

We also found increased gray matter volume at the right ventral striatum and putamen in CSU patients compared with HCs. Although there have been very few studies on brain structure changes in chronic itch patients, an increase of gray matter density and volume in the striatum has been reported in chronic pain<sup>47–50</sup>. The ventral striatum and putamen may be involved in the anticipation of itch, as well as in itch relief. The observed structural changes may be due to the altered function of the ventral striatum and putamen in CSU and compensatory responses to itch and to altered movement control.

To further explore the network involved in the right striatum, we used the ventral striatum and putamen as seeds and performed a resting state functional connectivity analysis. We found that CSU patients were associated with decreased rs-FC relative to HCs between the right putamen and left precentral gyrus. The precentral gyrus is the site of the primary motor cortex, which is the primary region of the motor system and works in association with other brain areas to plan and execute scratching movements<sup>51</sup>. Studies suggest that the primary motor cortex is related to itch processing<sup>10–14</sup>. The primary motor cortex and reward system are associated with motor control and motivational aspects of behavior in the itch-scratch cycle<sup>52</sup>. Scratching in chronic itch patients induces a more robust activation of motor-related regions and of the reward system<sup>52</sup>. The primary motor cortex projects to a portion of the striatum (mostly putamen), which in turn projects back to motor areas of the cortex by way of

the ventral anterior and ventral lateral (VA/VL) nuclei of the thalamus<sup>53,54</sup>. We thus speculate that the decreased connectivity between the putamen and primary motor cortex may reflect a disrupted motivation-motor process in chronic itch patients.

We also found that CSU is associated with decreased rs-FC relative to HCs between the right ventral striatum and right occipital cortex. The occipital cortex contains most of the anatomical regions of the visual cortex<sup>55</sup>. A study of mice found that scratching behavior can be induced not only by mere observation of conspecific scratching in a video, but also by artificially stimulating the suprachiasmatic nucleus GRPR neurons, which suggests that visual-related areas may constitute the neural circuits for itch<sup>40</sup>. Further study is needed to explore the role of occipital cortex in chronic itch.

## Conclusions

Using multiple-modality brain imaging tools, we found functional, structural and resting state functional connectivity alterations of the right ventral striatum and putamen in patients with CSU. Our results suggest that CSU may be associated with disrupted reward, motivation, and motor processing.

## Methods

This research protocol has been approved by the Institutional Ethics Committee of Guang'anmen Hospital affiliated with the China Academy of Chinese Medical Sciences. The experiment was performed in accordance with approved guidelines. All subjects signed the written informed consent before the study began.

**Subjects.** *CSU Patients.* Forty patients were recruited from the outpatient clinic in the department of dermatology at Guang'anmen Hospital. Patients with a documented history of CSU, characterized by transient, itchy wheals of unknown etiology, occurring regularly from 6 weeks or more before consent acquisition were enrolled in the study. All patients received non-sedation H1-antihistamines (such as Loratadine, Desloratadine, Fexofenadine, Cetirizine dihydrochloride) before enrollment.

Inclusion criteria were: 18 to 60 years old; a UAS<sup>76</sup> > 14; right handed; have a clear asymptomatic stage more than three hours during the day without non-sedating H1-antihistamine treatment.

Exclusion criteria were: use of sedating antihistamines (such as Alimemazine, Chlorphenamine, Clemastine, Cyproheptadine, Hydroxyzine, Ketotifen, Promethazine), corticosteroids, biologics, psychotropic drugs, or opioids in the past 3 months; chronic pain; pregnant or lactating women; current or history of psychiatric or neurological diseases, head trauma, or loss of consciousness; claustrophobia; metal implants; other skin diseases.

*Healthy controls (HCs).* Forty right-handed HCs were gender and age matched with CSU patients.

*Clinical Outcome assessment.* Clinical symptoms were assessed using the UAS<sup>77</sup> and acquired about three days before the fMRI scan.

*Magnetic resonance imaging data acquisition.* Patients who were taking non-sedating antihistamines discontinued them three days prior to the scan. During the scan, patients did not have any itching or wheals.

Functional MRI was conducted on a 3.0 T Siemens MAGNETOM Skyra MRI system equipped with a standard twenty-channel head coil. Foam pads were used to restrict head motion. T2WI data was acquired to exclude the lesion and abnormality. T1-weighted high resolution structural images were acquired with the three dimensional fast spoiled gradient-echo sequence (TR 5000 ms, TE 2.98 ms, matrix 256 × 256, FOV 256 × 240 mm, FA 1 = 4°, slice thickness 1 mm, gap 0 mm, 176 slices). BOLD fMRI images encompassing the whole brain were collected with the gradient echo EPI sequence (TR 2500 ms, TE 30 ms, matrix 70 × 70, FOV 210 × 210 mm, FA = 90°, slice thickness 3 mm, gap 0 mm, 43 slices, paralleled by AC-PC line). During the 369 second (dummy scan for the first 9 seconds) resting state fMRI scan, subjects were asked to lie still with their eyes closed.

**Statistical analysis.** *Behavioral data.* Statistical analyses were performed using SPSS 18.0 (SPSS Inc, Chicago, IL). The mean ± SD were calculated for normally distributed continuous variables.

*Data preprocessing and Calculation of ALFF.* Data preprocessing and calculation of ALFF was performed using DPARSF software of Dpabi V2.3 (a toolbox for Data Processing and Analysis of brain imaging; <http://rfmri.org/dpabi>)<sup>58</sup>, which is based on Statistical Parametric Mapping 12 (SPM12) and the Resting-state fMRI Data Analysis Toolkit (<http://www.restfmri.net>)<sup>59</sup> in MATLAB (MathWorks, Natick, MA, USA).

We first checked the scanning image quality for each participant and transformed EPI DICOM to NIFTI. We removed the first 4 time points and then functional slice-timing corrected, spatially realigned, segmented the structural image into gray matter, white matter and cerebrospinal fluid (CSF), removed the friston 24 head motion parameters and CSF signals as regressors, and normalized the images using standard Montreal Neurological Institute (MNI) templates with a resolution of 3 × 3 × 3 mm. Subjects with head movements exceeding 2 mm on any axis or with head rotation greater than 2° were excluded and smoothed with a Gaussian kernel of 8-mm full-width at half maximum (FWHM). Lastly, the time series for each voxel was filtered (bandpass, 0.01–0.08 Hz) to remove the effects of very-low-frequency drift and high frequency noise.

ALFF calculations were based on previous studies<sup>60</sup>. For a given voxel, a fast Fourier transform (FFT) (parameters: taper percent = 0, FFT length = shortest) was used to convert the filtered time series to a frequency domain to obtain the power spectrum. The power spectrum was then square-rooted and averaged across 0.01–0.08 Hz at each voxel, which was deemed as the ALFF. Ultimately, we obtained each participant's Z-standardized ALFF map for the following statistical analysis.

SPM12 was used to examine group differences. Two-sample t-tests were performed between HCs and CSU patients. A threshold of voxel-wise  $p < 0.005$  uncorrected and  $p < 0.05$  cluster-level family-wise error rate (FWE) corrected was applied for ALFF analysis.

**Voxel-based morphometry (VBM) analysis.** VBM analyses were carried out in SPM12. Similar to our previous studies<sup>61</sup>, the T1 images were first segmented into grey matter (GM), white matter and cerebrospinal fluid (CSF) and normalized using the high dimensional DARTEL algorithm<sup>62</sup>. To reduce variability between the subjects, we created a group specific template. Then, the template was used to normalize the images into the standard Montreal Neurological Institute (MNI) space with an isotropic Gaussian kernel of 8 mm full-width at half maximum. Group analysis was applied using two sample t-tests. An absolute threshold of 0.1 was used for masking<sup>61,63</sup>. Total intracranial volume was obtained by summing up the overall volumes of GM, white matter, and CSF.

In this study, we only focused on the VBM changes in the right ventral striatum / putamen (region of interest) as revealed by ALFF analysis. Small volume correction with a threshold of voxel-wise  $p < 0.005$  (uncorrected) and  $p < 0.05$  FWE corrected at cluster level was applied.

**Data preprocessing and Calculation of Seed-based Function connectivity.** Data preprocessing and calculations of functional connectivity were all carried out using the CONN-fMRI Functional Connectivity toolbox v17.c<sup>64</sup> (<http://www.nitrc.org/projects/conn>), which is based on SPM12 in MATLAB. We used the default preprocessing pipeline for volume-based analysis (direct normalization to MNI-space). The specific steps are as follows: functional realignment and unwarping; functionally centered to coordinates; functional slice-timing corrected; structural center to coordinates; structural segmentation and normalization; functional normalization; functional outlier detection (ART-based identification of outlier scans for scrubbing); functional smoothing with an 8-mm FWHM. Band-pass filtering was performed using the low frequency band (0.01–0.08 Hz).

Seeds were chosen based on the VBM results (right ventral striatum and right putamen), which indicate the overlap area in both ALFF and VBM analysis. Functional connectivity measures were computed between each seed and every other voxel in the brain. The residual BOLD time course was extracted from a given seed and then its first-level correlation map was estimated by computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were transformed into Fisher's 'Z'-scores to increase normality and allow for improved second-level General Linear Model analyses. Seed-to-voxel functional connectivity was estimated for each subject.

SPM12 was used to examine group differences. Two-sample t-tests were performed between HCs and CSU. A threshold of voxel-wise  $p < 0.005$  uncorrected and cluster-level  $p \leq 0.05$  FWE corrected was applied for rs-FCD data analysis.

## References

- Zuberbier, T. *et al.* The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update. *Allergy Eur. J. Allergy Clin. Immunol.* **69**, 868–887 (2014).
- Maurer, M. *et al.* Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. *Allergy: European Journal of Allergy and Clinical Immunology* **66**, 317–330 (2011).
- Baiardini, I. *et al.* Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* **58**, 621–3 (2003).
- Slominski, A. T. *et al.* Sensing the environment: Regulation of local and global homeostasis by the skin's neuroendocrine system. *Anat. Embryol. Cell Biol.* **212**, 1–115 (2012).
- Mueller, S. M. *et al.* Functional magnetic resonance imaging in dermatology: The skin, the brain and the invisible. *Experimental Dermatology* **26**, 845–853 (2017).
- Kim, J. E., Cho, B. K., Cho, D. H. & Park, H. J. Expression of Hypothalamic-pituitary-adrenal axis in common skin diseases: Evidence of its association with stress-related Disease Activity. *Acta Dermato-Venereologica* **93**, 387–393 (2013).
- Arck, P. & Paus, R. From the brain-skin connection: The neuroendocrine-immune misalliance of stress and itch. *Neuro Immuno Modulation* **13**, 347–356 (2007).
- Puxeddu, I., Pratesi, F., Ribatti, D. & Migliorini, P. Mediators of Inflammation and Angiogenesis in Chronic Spontaneous Urticaria: Are They Potential Biomarkers of the Disease? *Mediators of Inflammation* **2017** (2017).
- Mochizuki, H. & Kakigi, R. Itch and brain. *Journal of Dermatology* **42**, 761–767 (2015).
- Mochizuki, H. & Kakigi, R. Central mechanisms of itch. *Clinical Neurophysiology* **126**, 1650–1660 (2015).
- Hsieh, J. C. *et al.* Urge to scratch represented in the human cerebral cortex during itch. *J. Neurophysiol.* **72**, 3004–8 (1994).
- Mochizuki, H. *et al.* Imaging of central itch modulation in the human brain using positron emission tomography. *Pain* **105**, 339–346 (2003).
- Drzeczga, A. *et al.* Central activation by histamine-induced itch: Analogies to pain processing: A correlational analysis of O-15 H<sub>2</sub>O positron emission tomography studies. *Pain* **92**, 295–305 (2001).
- Leknes, S. G. *et al.* Itch and motivation to scratch: an investigation of the central and peripheral correlates of allergen- and histamine-induced itch in humans. *J Neurophysiol* **97**, 415–422 (2007).
- Biswal, B. B. Resting state fMRI: A personal history. *NeuroImage* **62**, 938–944 (2012).
- Fox, P. T. *et al.* BrainMap taxonomy of experimental design: Description and evaluation. In *Human Brain Mapping* **25**, 185–198 (2005).
- Snyder, A. Z. & Raichle, M. E. A brief history of the resting state: The Washington University perspective. *NeuroImage* **62**, 902–910 (2012).
- Fox, M. D. & Raichle, M. E. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* **8**, 700–711 (2007).
- Zang *et al.* Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev* **29**, 83–91 (2007).
- Yan, C. G., Craddock, R. C., Zuo, X. N., Zang, Y. F. & Milham, M. P. Standardizing the intrinsic brain: Towards robust measurement of inter-individual variation in 1000 functional connectomes. *Neuroimage* **80**, 246–262 (2013).
- Xue, T. *et al.* Alterations of regional spontaneous neuronal activity and corresponding brain circuit changes during resting state in migraine without aura. *NMR Biomed.* **26**, 1051–1058 (2013).
- Qi, R. *et al.* Intrinsic brain abnormalities in irritable bowel syndrome and effect of anxiety and depression. *Brain Imaging Behav.* <https://doi.org/10.1007/s11682-015-9478-1> (2015).

23. Wang, J.-J. *et al.* Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF in migraine patients: a resting-state functional MRI study. *Clin. Radiol.* **71**, 558–64 (2016).
24. Li, Z. *et al.* Acupuncture modulates the abnormal brainstem activity in migraine without aura patients. *NeuroImage Clin.* **15**, 367–375 (2017).
25. Papoiu, A. D. P. *et al.* Voxel-based morphometry and arterial spin labeling fMRI reveal neuropathic and neuroplastic features of brain processing of itch in end-stage renal disease. *J. Neurophysiol.* **112**, 1729–1738 (2014).
26. Maurer, M., Ortonne, J. P. & Zuberbier, T. Chronic urticaria: An internet survey of health behaviours, symptom patterns and treatment needs in European adult patients. *Br. J. Dermatol.* **160**, 633–641 (2009).
27. Middleton, F. A. Basal-ganglia 'Projections' to the Prefrontal Cortex of the Primate. *Cereb. Cortex* **12**, 926–935 (2002).
28. Haber, S. N. The primate basal ganglia: Parallel and integrative networks. in: *Journal of Chemical Neuroanatomy* **26**, 317–330 (2003).
29. Olsen, C. M. Natural rewards, neuroplasticity, and non-drug addictions. *Neuropharmacology* **61**, 1109–1122 (2011).
30. Yu, R. *et al.* Placebo analgesia and reward processing: Integrating genetics, personality, and intrinsic brain activity. *Hum. Brain Mapp.* **35**, 4583–4593 (2014).
31. Papoiu, A. D. P., Kraft, R. A., Coghill, R. C. & Yosipovitch, G. Butorphanol suppression of histamine itch is mediated by nucleus accumbens and septal nuclei: A pharmacological fMRI study. *J. Invest. Dermatol.* **135**, 560–568 (2015).
32. Costa, V. D., Lang, P. J., Sabatinelli, D., Versace, F. & Bradley, M. M. Emotional imagery: Assessing pleasure and arousal in the brain's reward circuitry. *Hum. Brain Mapp.* **31**, 1446–1457 (2010).
33. Sabatinelli, D., Bradley, M. M., Lang, P. J., Costa, V. D. & Versace, F. Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *J. Neurophysiol.* **98**, 1374–9 (2007).
34. O'Neill, J. L., Chan, Y. H., Rapp, S. R. & Yosipovitch, G. Differences in itch characteristics between psoriasis and atopic dermatitis patients: Results of a web-based questionnaire. *Acta Derm. Venereol.* **91**, 537–540 (2011).
35. Bin Saif, G. A. *et al.* The pleasurability of scratching an itch: A psychophysical and topographical assessment. *Br. J. Dermatol.* **166**, 981–985 (2012).
36. Papoiu, A. D. P. *et al.* Brain's reward circuits mediate itch relief. A functional MRI study of active scratching. *PLoS One* **8** (2013).
37. Mochizuki, H. *et al.* The cerebral representation of scratching-induced pleasantness. *J. Neurophysiol.* 488–498, <https://doi.org/10.1152/jn.00374.2013> (2013)
38. Vierow, V., Forster, C., Vogelgsang, R., Dörfler, A. & Handwerker, H. O. Cerebral networks linked to itch-related sensations induced by histamine and capsaicin. *Acta Derm. Venereol.* **95**, 645–652 (2015).
39. Kleyn, C. E., McKie, S., Ross, A., Elliott, R. & Griffiths, C. E. A temporal analysis of the central neural processing of itch. *Br J Dermatol* **166**, 994–1001 (2012).
40. Yu, Y.-Q. *et al.* Molecular and neural basis of contagious itch behavior in mice. *Science (80-.)*. **355**, 216–217 (2017).
41. Graybiel, A. M. Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.* **31**, 359–387 (2008).
42. Desbordes, G. *et al.* Evoked itch perception is associated with changes in functional brain connectivity. *NeuroImage Clin.* **7**, 213–221 (2015).
43. Vierow, V. *et al.* Cerebral representation of the relief of itch by scratching. *J. Neurophysiol.* **102**, 3216–24 (2009).
44. Papoiu, A. D. P., Coghill, R. C., Kraft, R. A., Wang, H. & Yosipovitch, G. A tale of two itches. Common features and notable differences in brain activation evoked by cowhage and histamine induced itch. *Neuroimage* **59**, 3611–3623 (2012).
45. Napadow, V. *et al.* The brain circuitry mediating antipruritic effects of acupuncture. *Cereb. Cortex* **24**, 873–882 (2014).
46. Kim, H. J., Park, J. B., Lee, J. H. & Kim, I. H. How stress triggers Itch: A preliminary study of the mechanism of stress-induced pruritus using fMRI. *Int. J. Dermatol.* **55**, 434–442 (2016).
47. Schmidt-Wilcke, T. *et al.* Striatal grey matter increase in patients suffering from fibromyalgia—a voxel-based morphometry study. *Pain* **132**(Suppl), S109–16 (2007).
48. Schmidt-Wilcke, T. *et al.* Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain* **125**, 89–97 (2006).
49. Schweinhardt, P., Kuchinad, A., Pukall, C. F. & Bushnell, M. C. Increased gray matter density in young women with chronic vulvar pain. *Pain* **140**, 411–419 (2008).
50. Wartolowska, K. *et al.* Structural changes of the brain in rheumatoid arthritis. *Arthritis Rheum.* **64**, 371–379 (2012).
51. Valet, M. *et al.* Cerebral processing of histamine-induced itch using short-term alternating temperature modulation—an FMRI study. *J. Invest. Dermatol.* **128**, 426–33 (2008).
52. Mochizuki, H. *et al.* Scratching Induces Overactivity in Motor-Related Regions and Reward System in Chronic Itch Patients. *J. Invest. Dermatol.* **135**, 2814–2823 (2015).
53. Künzle, H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in Macaca fascicularis. *Brain Res.* **88**, 195–209 (1975).
54. Shipp, S. The functional logic of corticostriatal connections. *Brain Structure and Function* **222**, 669–706 (2017).
55. Quintero, G. C. Advances in cortical modulation of pain. *Journal of Pain Research* **6**, 713–725 (2013).
56. Mlynek, A. *et al.* How to assess disease activity in patients with chronic urticaria? *Allergy* **63**, 777–780 (2008).
57. Zuberbier, T. *et al.* EAACI/GA2LEN/EDF/WAO guideline: Definition, classification and diagnosis of urticaria. *Allergy Eur. J. Allergy Clin. Immunol.* **64**, 1417–1426 (2009).
58. Yan, C. G., Wang, X., Di, Zuo, X. N. & Zang, Y. F. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics* **14**, 339–351 (2016).
59. Song, X.-W. *et al.* REST: A Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing. *PLoS One* **6**, e25031 (2011).
60. Yang, H. *et al.* Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage* **36**, 144–152 (2007).
61. Tao, J. *et al.* Ta Chi Chuan and Baduanjin increase grey matter volume in older adults: a brain imaging study. *J. Alzheimer's Dis.* (2017).
62. Ashburner, J. A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95–113 (2007).
63. Kalmady, S. V. *et al.* Relationship between Interleukin-6 gene polymorphism and hippocampal volume in antipsychotic-naive schizophrenia: evidence for differential susceptibility? *PLoS One* **9**, e96021 (2014).
64. Whitfield-Gabrieli, S. & Nieto-Castanon, A. Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connect.* **2**, 125–141 (2012).

## Acknowledgements

The work is supported by the Fundamental Research Funds for the Central Public Welfare Research Institutes, China Academy of Chinese Medical Sciences (ZZ0908054), the foundation of Guang'anmen Hospital (2015s323), and the China Postdoctoral Science Foundation (grant No. 2017M611121). Jian Kong is supported by R01AT006364, R01AT008563, R61AT009310, R21AT008707 and P01 AT006663 (NIH/NCCIH).

### Author Contributions

Y.M.W. performed the experimental design, analyzed the data and made the manuscript preparation; J.K., J.L., analyzed the data and made the manuscript preparation; J.L.F., B.N.C., P.S., performed the experimental design and collected the data; C.L. made the manuscript preparation; Y.B., C.C.X., X.D., Z.F.Y., Y.H.Y., Q.K., collected the data; R.R.S., analyzed the data. All authors contributed to drafting the manuscript and have read and approved the final manuscript.

### Additional Information

**Competing Interests:** J.K. has a disclosure to report (holding equity in a startup company (MNT) and a pending patent to develop a new neuromodulation device) but declares no conflict of interest. All other authors declare no conflict of interest.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2018