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Neural Correlates of Self-Injurious Behavior in Prader–Willi Syndrome

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Abstract: Individuals with Prader–Willi syndrome (PWS), a genetic disorder caused by mutations to the q11-13 region on chromosome 15, commonly show severe skin-picking behaviors that can cause open wounds and sores on the body. To our knowledge, however, no studies have examined the potential neural mechanisms underlying these behaviors. Seventeen individuals with PWS, aged 6–25 years, who showed severe skin-picking behaviors, were recruited and scanned on a 3T scanner. We used functional magnetic resonance imaging (fMRI) while episodes of skin picking were recorded on an MRI-safe video camera. Three participants displayed skin picking continuously throughout the scan, three participants did not display skin picking, and the data for one participant evidenced significant B0 inhomogeneity that could not be corrected. The data for the remaining 10 participants (six male, four female) who displayed a sufficient number of picking and nonpicking episodes were subjected to fMRI analysis. Results showed that regions involved in interoceptive, motor, attention, and somatosensory processing were activated during episodes of skin-picking behavior compared with nonpicking episodes. Scores obtained on the Self-Injury Trauma scale were significantly negatively correlated with mean activation within the right insula and left precentral gyrus. These data indicate that itch and pain processes appear to underlie skin-picking behaviors in PWS, suggesting that interoceptive disturbance may contribute to the severity and maintenance of abnormal skin-picking behaviors in PWS. Implications for treatments are discussed. *Hum Brain Mapp 36:4135–4143, 2015.*

Key words: functional magnetic resonance imaging; repetitive behavior; developmental disability; interoception; genetic disorder

INTRODUCTION

Prader–Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by paternal deletion (DEL) of genes in the 15q11-13 region in 70% of cases, maternal uniparental disomy (UPD) of chromosome 15 in approximately 25% of cases, or other mutations that inactivate genes in the 15q11-13 region in 5% of cases [Didden et al., 2007; Smith et al., 2003; Vogels et al., 2004; Whittington et al., 2001]. In addition to homogeneous physical characteristics and facial features, approximately 60–85% of individuals with PWS display severe skin-picking behaviors [Didden et al., 2007; Wigren and Heimann, 2001] including scratching, picking and/or poking at scabs, blemishes, and

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other skin abnormalities to the point of developing significant skin damage and wounds [Hustyi et al., 2013]. Although several studies have examined the prevalence, frequency, severity, and forms of skin picking shown by individuals with PWS, the neural mechanisms underlying chronic skin picking in PWS are currently unknown.

One theory concerning the mechanisms underlying chronic skin picking in PWS suggests that there might be a significant relationship between skin-picking behaviors and pain processing [Schroeder et al., 2001]. For example, impaired peripheral somatosensory nerve fiber action potential amplitudes [Brandt and Rosen, 1998] and high pain thresholds—as measured by quantitate sensory testing (QST)—have been detected in PWS [Priano et al., 2009], suggesting that individuals with PWS may have impaired pain processing. Pain is one aspect of interoceptive functioning, which is defined as the receiving, processing, and integration of body-relevant signals with external stimuli and its effect on ongoing, motivated behavior [Craig, 2002]. Interoception is processed within the insula, which is considered the interoceptive cortex of the brain. Thus, the theory connecting skin picking to abnormal pain processing implies that interoceptive disturbance may also contribute to the symptoms displayed in PWS.

Pain plays an important role in interoceptive regulation and is one of many body-relevant cues that are associated with interoceptive processing. These cues also include: itch, hunger, satiety, sensual touch, and the need to breathe, urinate, and defecate [Craig, 2002; de Groat, 1981; Kanazawa et al., 2010; Yoshimura et al., 2006]. These interoceptive cues provide feedback about one's internal, physiological regulation [Craig, 2003; Denton, 2006] and signal that certain behaviors or compensatory acts are necessary to maintain adequate homeostasis [Denton, 2006]. Studies suggest that there is an integral link between itch and pain processing [LaMotte et al., 2014]. Brain regions activated by itch and pain are nearly identical; itch activates somatosensory, interoceptive, attention, motor, and reward processing regions while similar regions are also activated during pain processing [Davidson and Giesler, 2010; Handwerker and Schmelz, 2009; LaMotte et al., 2014]. Scratching (a behavior signaled by the sensation of itch) activates motor and somatosensory regions and deactivates regions involved in interoceptive, attention, and reward processing [Mochizuki et al., 2014; Papoiu et al., 2013; Vierow et al., 2009; Yosipovitch et al., 2008].

Itch and pain processing may thus play an important role in the skin-picking behaviors displayed in PWS. Skin-picking behaviors may initially occur in response to a physiological event such as itch sensation and serve the purpose of rebalancing an individual's internal homeostasis [Hall et al., 2013; Kern et al., 2003; Lovaas et al., 1987]. Thus, interoceptive disturbance may either distort the internal stimuli's signal strength (such as the strength of the sensation of itch and the relief of itch provided by scratching) and/or the experience of pain. The possibility that individuals with PWS have high pain thresholds also suggests that skin-picking behaviors may continue even after becoming harmful, and, thus, lead to significant skin damage.

To better understand how severe skin-picking behaviors are processed within the brain, we used functional magnetic resonance imaging (fMRI) and observed participants with PWS as they spontaneously engaged in skin-picking while in the scanner. As motor, somatosensory, interoceptive, attention, and reward regions are associated with itch and scratching behaviors, we hypothesized that these regions would be activated to a greater extent during spontaneous skin-picking episodes as compared with non-picking episodes.

MATERIALS AND METHODS

Recruitment and Screening

Participants were recruited throughout the United States and Canada via the Prader–Willi Syndrome Association (USA), the Foundation for Prader–Willi Research and PWS-specific parent groups. A trained research assistant used a phone screen to determine participant eligibility, the severity, and potential function of skin-picking behavior and to document any currently prescribed medications. During the phone screen, caregivers of the participants completed the Self-Injury Trauma (SIT) Scale [Iwata et al., 1990]. The SIT Scale is a rating scale designed to quantify surface tissue damage resulting from self-injury. The SIT Scale was completed in-person at the time of participation by having two observers (i.e., the therapist and caregiver) examine the participant for current wounds. The caregiver was also asked to report any wounds that were not readily visible. The Number Index (NI) yields a score from 0 to 5, with a score of 0 indicating no injuries and a score of 5 representing 17 or more injuries. The Severity Index (SI) yields a score from 0 to 5, with a score of 0 reflecting no injuries and a score of 5 representing multiple, deep, or extensive breaks in the skin.

Participants were included in the study if they had a confirmed diagnosis of PWS, were aged between 6 and 25 years, engaged in skin-picking on a daily basis, and obtained a SI score of 2 or higher on the SIT Scale [see Table I for demographic information]. Thirteen participants had taken part in the study by Hall et al. [2014] in which skin picking was observed under a variety of environmental conditions (i.e., ignore, alone, attention, demand, and play). In that study, skin picking occurred primarily during the ignore and/or alone conditions, indicating that the behavior was not maintained by social consequences. Participants were excluded from this study if they primarily engaged in skin picking on the face and/or neck, exhibited excessive daily sleepiness, and presented with MRI contraindications such as metal in the body or

claustrophobia. All procedures were approved by the Institutional Review Board at Stanford University and all participants and parents consented and assented prior to study participation.

Seventeen participants (11 male, 6 female) met the study inclusion criteria and travelled to Stanford for scans. The mean age of the participants was 15.7 years (SD = 4.8), the mean intelligence quotient (IQ) was 70.9 (SD = 10.0), and the mean body mass index (BMI) was 26.4 (SD = 5.9). Six participants had the UPD subtype and 11 participants had the DEL subtype. The mean NI score on the SIT Scale was 3.3 (SD = 1.4). As a group, there were no associations between age, IQ, BMI, and NI score. There were also no differences between those with the UPD and Deletion subtype on these variables. However, male participants had significantly higher BMI scores than female participants, ($t(15) = 3.4$, $P = 0.004$).

Procedures

All participants were scanned at Stanford University's Center for Cognitive and Neurobiological Imaging using a 3.0 T General Electric Healthcare whole body MR system (GE Healthcare Systems, Milwaukee, WI) and a standardized head coil. A high-resolution anatomical pulse sequence was used for localization and coregistration of functional data (TR = 7.9 s, TE = 3.06 ms, flip angle =12°, matrix 256 × 256 pixels, FOV = 24 × 240 mm^2). A T2-weighted gradient echo planar pulse sequence was used to obtain functional images (TR = 2 s, TE = 30 ms, flip angle = 77°, matrix 80 × 80 pixels, FOV = 232 × 232 mm^2, slice thickness = 2.9 mm, slice gap = 0 mm). For the first two participants, scans lasted for 610 s (305 volumes). For the remaining participants, scans lasted for 310 s (155 volumes). A higher order shimming protocol was used prior to functional scans to correct for B0 heterogeneity and to avoid blurring and signal loss [Kim et al., 2002]. Each participant's head was immobilized using a custom-built head stabilizer to minimize head movement during the scan. A custom made MRI-scanner safe video camera was used to record in-scanner skin-picking behaviors. After each subject had been positioned into the bore of the scanner, the camera was attached to the foot of the scanner table so that the participant's body and hands could be viewed. The live feed of the video was projected onto a monitor in the console room. In this way, the subject was not aware that his/her skin-picking behavior was being recorded. However, the scanner operator could see whether the subject was engaging in skin-picking at any time.

After completing a structural scan, shim, and localizer, participants were told via the scanner intercom that they could engage in skin picking if they wanted to and that no disapproval from parents or staff would occur. Between three and six scans were obtained for each participant until at least one scan contained episodes of skin picking and nonpicking. Prior to each scan, the subject was reminded that he/she could engage in skin picking at any time and between each scan, the subject was asked if he/she was feeling ok, and if it was ok to continue. Once all scans had been completed, any wounds or sores that had occurred during the scans were subsequently cleaned and dressed with bandages.

fMRI Data Analysis

Functional imaging data were analyzed and preprocessed using FSL's FEAT (FMRI Expert Analysis Tool) Version 6.00. The following preprocessing steps were applied: motion correction using MCFLIRT, nonbrain removal using AFNI skull stripping, spatial smoothing using a Gauassian kernel of FWHM 5 mm, grand mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and highpass temporal filtering (Guassian-weighted least-squares straight line fitting). Registration to high-resolution structural and standard space images were performed using FLIRT. Time series statistical analyses were performed using FILM with local autocorrelation correction.

Motion Analysis

Given the possibility for increased skin-picking behavior related motion, various sources of motion were regressed out of the general linear model. In addition to regressing out the six motion parameters included within the FSL package, we also applied "data scrubbing" procedures as described by Power et al. using the FSL motion outliers' script [Power et al., 2012]. During data scrubbing, the union between the root mean squared intensity differences of volume N to volume $N + 1$ (DVARS; rotation average) and frame displacement (FD; translation parameter differences) were added as additional confound explanatory variables and, thus, were regressed out of our linear model. The cut-off threshold for FD and DVARS were computed automatically using the 75th percentile + 1.5 times the interquartile range, as implemented in the *fsl_motion_outliers* script (supplied with FSL). Additionally, 1 volume before and 2 volumes after the union of DVARS and FD were also excluded [Power et al., 2012].

Individual Subject Analyses

Skin-picking related brain activation was identified using a general linear model. In-scanner videos of participant skin-picking behaviors were coded for the onset and offset of skin picking on a second-by-second analysis. The onset of skin picking was defined as any observable back and forth movement of the participants' index or middle finger of the hand against another body part. The offset of skin picking was defined as the absence of skin picking for at least 2 s. Onset and offset times of skin picking were

TABLE I. Demographic characteristics of participants with PWS

Subject	Age	Sex	IQ	BMI	Form of PWS	SIT scale Number Index	SIT scale Severity Index
1	17.5	Male	64	22.8	UPD	1	3
2	17.7	Male	64	37.4	UPD	2	5
3	18.8	Male	58	28.4	Deletion	3	5
4	22.1	Female	79	21.0	Deletion	1	5
5	11.9	Male	60	31.9	Deletion	4	5
6	15.0	Male	63	33.6	Deletion	4	5
7	10.5	Female	67	16.7	Deletion	3	5
8	6.3	Female	71	25.3	Deletion	3	5
9	11.0	Female	87	26.7	UPD	3	4
10	15.8	Male	92	27.5	Deletion	5	5
11	13.9	Female	75	19.1	UPD	5	5
12	18.1	Male	55	34.0	Deletion	5	5
13	23.8	Male	78	27.5	Deletion	5	5
14	15.8	Male	69	23.0	UPD	1	2
15	24.0	Female	76	19.3	Deletion	3	5
16	12.9	Male	77	24.1	Deletion	3	5
17	12.5	Male	70	30.3	UPD	5	5

IQ = intelligence quotient; UPD = uniparental disomy; BMI = Body Mass Index.

entered into the general linear model as explanatory variables. Onsets for picking and nonpicking periods were convolved using a double gamma hemodynamic response function. Contrasts included picking > nonpicking and nonpicking > picking. A temporal derivative was additionally used to account for voxel-wise differences in the hemodynamic response and temporal filtering was applied. Voxel-wise t-statistics maps for each comparison were generated for each participant.

Random Effects

Z Guassianized T/F statistic images were thresholded using clusters determined by $Z > 1.96$ and cluster-corrected at FWER of $P = 0.05$. Demeaned age was added into random effects analyses as a nuisance covariate. Brain regions were converted from MNI space to Talairach x, y, and z coordinates and subsequently confirmed on the Talairach atlas.

Correlation Analyses

From the picking > nonpicking contrast maps, we selected the highest activated voxels and drew 5 mm spheres around them to create activation masks. These masks included: the right and left anterior cingulate cortex, left and right insula, right paracingulate, the left parietal operculum, right postcentral gyrus, the left precentral gyrus, the left posterior cingulate, and the right superior frontal gyrus. The mean parameter estimates (or beta values) for the picking > nonpicking contrast were extracted for each mask with the *FEATQuery* script (also supplied by FSL). Using the Spearman rho statistic, the mean activation for each ROI was correlated with IQ, BMI, and SIT Scale NI score.

RESULTS

After participating in the scans, one participant (subject 17) was excluded from the analyses as the scans demonstrated significant B0 inhomogeneity that we were unable to correct, and three participants (subjects 12, 14, and 16) were excluded because they did not engage in skin picking during any of the scan runs. Three additional participants (subjects 11, 13, and 15) engaged in skin picking continuously during all scan runs and these participants were, therefore, also excluded from analyses as skin-picking offsets were needed to conduct fMRI analyses. The mean age of the 10 participants that were included in the analyses was 14.7 years (SD = 4.7 years), the average IQ was 70.5 (SD = 11.7), and the mean BMI was 27.1 (SD = 6.2). The mean NI score on the SIT Scale was 2.9 (SD = 1.3). Eight participants obtained a SI of 5 on the SIT Scale, indicating that their skin picking was severe.

During each scanner session, participants engaged in skin picking for an average of 57.0% (SD = 0.24, range = 14–85) of the time. The average length of the participants' skin-picking episodes was 33.6 s (SD = 26.3 s, range 12.2–86.5 s) and the average length of nonpicking episodes was 29.4 s (SD = 21.6 s, range = 12.0–64.5 s). The mean relative head displacement was 0.47 mm (SD = 0.41) across the 10 participants and a mean of 29% of TRs (SD = 7%) were removed after data scrubbing procedures detected significant motion (See Table II).

Neuroimaging Results

Brain activation during picking episodes was contrasted with brain activation during nonpicking episodes. Using this contrast, increased activity during skin picking was observed in two clusters. These clusters were corrected at

TABLE II. In-scanner skin-picking behavior characteristics and participant in-scanner head movement characteristics

Subject	Form of skin-picking	Hand used	Percentage skin-picking observed[a]	Relative head motion (mm)[b]	Proportion of TRs removed[c]	Episode length (s)	Interepisode length (s)
1	Toe, hand	Right	85%	0.96	0.33	86.5	18.0
2	Finger, hand	Both	48%	0.11	0.18	12.2	20.5
3	Hand	Both	22%	1.27	0.28	17.0	60.3
4	Arm	Right	42%	0.38	0.42	8.6	12.0
5	Hand	Both	65%	0.53	0.32	28.7	15.1
6	Finger	Right	64%	0.08	0.26	66.3	55.0
7	Face	Right	87%	0.11	0.24	54.8	8.0
8	Arm and face	Both	42%	0.53	0.31	21.0	64.5
9	Arm	Left	14%	0.22	0.32	25.4	17.4
10	Hand and leg	Both	41%	0.31	0.24	15.9	22.8

[a]Percentage skin-picking was calculated by dividing the time participants spent engaged in skin-picking by the length of the entire run.
[b]Relative head motion was calculated by FSL's MCFLIRT motion correction.
[c]Proportion of TRs removed due to excessive motion was determined by a data scrubbed procedure detailed in Power et al. [2012]. Motion outliers were determined by FD and DVARS; one TR before the union between the two measures and two TRs after were regressed out of the GLM model. Proportion removed was calculated by dividing the number of TRs removed by the total TRs in each run.

$Z = 1.96$ and had a family wise error rate of $P = 0.05$. The first cluster encompassed the bilateral postcentral gyrus (the primary somatosensory cortex), left inferior parietal lobule, left paracentral lobule (covering the supplementary motor area), and left middle frontal gyrus. Other regions that were partially encompassed by this cluster included the right posterior insula (MNI coordinates, $x = -42$, $y = -16$, and $z = 8$; Z-max = 2.33) and the left claustrum (MNI coordinates, $x = 34$, $y = -2$, and $z = 8$; Z-max = 2.77). The second cluster from the picking versus nonpicking contrast included right lateralized regions of the anterior cingulate and middle frontal gyrus. Figure 1 presents activation maps presented on an inflated MNI brain. Table III presents the statistical information, local maxima locations (in Talairach space), and the corresponding Brodmann Areas within each cluster. For the reverse contrast, that is, nonpicking > picking, no significant activation at the cluster-corrected $Z = 1.96$ and FWER of $P = 0.05$ was observed.

Simultaneous activation within the somatosensory (S1) and primary/supplementary motor cortices during skin-picking episodes indicated that the primary somatosensory and motor cortex were integrally involved in skin picking. Activation during skin-picking episodes overlapped within the left homunculus, specifically the hand and arm regions on the premotor and motor sulcus. These findings would be expected given that participants primarily engaged in skin picking at the hand, arm, and face regions (See Table III).

Correlation Analyses

To determine whether IQ, BMI, and/or skin-picking severity were associated with brain activation within particular brain regions, we conducted a correlation analysis. We found that the mean activation within the right insula and the SIT scale NI score was significantly negatively correlated (Spearman rho = −0.68, $P = 0.05$) (see Fig. 2a). Mean activation within the left precentral gyrus and the SIT scale NI score was also significantly negatively correlated (Spearman rho = −0.85, $P = 0.004$) (see Fig. 2b). No significant relationships between IQ, BMI, and mean activation across ROIs were found.

DISCUSSION

To our knowledge, this is the first study to examine the neural correlates of spontaneous skin-picking behaviors in PWS using fMRI. Ten of 17 individuals (58.8%) displayed skin-picking and nonpicking episodes within the same scanner run and, thus, these data could be subjected to fMRI analyses. As predicted, we found that skin-picking behaviors activated regions involved in interoceptive, motor, attention, and somatosensory processing; the same regions activated during itch/scratching behaviors and pain processing [Leknes et al., 2007; Mochizuki et al., 2014; Papoiu et al., 2013; Vierow et al., 2009; Yosipovitch et al., 2008]. Previous studies have shown that individuals with PWS may demonstrate abnormal pain processing [Brandt and Rosen, 1998] and potentially higher pain thresholds than controls [Priano et al., 2009], increased functional connectivity across the anterior cingulate/insula and frontal regions [Zhang et al., 2013], as well as abnormal GABA (A) receptor binding within the insula [Lucignani et al., 2004]. Therefore, abnormal interoceptive dysfunction (as evidenced by pain studies) and abnormal function within interoceptive circuits have been previously detected in PWS. Our study results suggest that functional activation

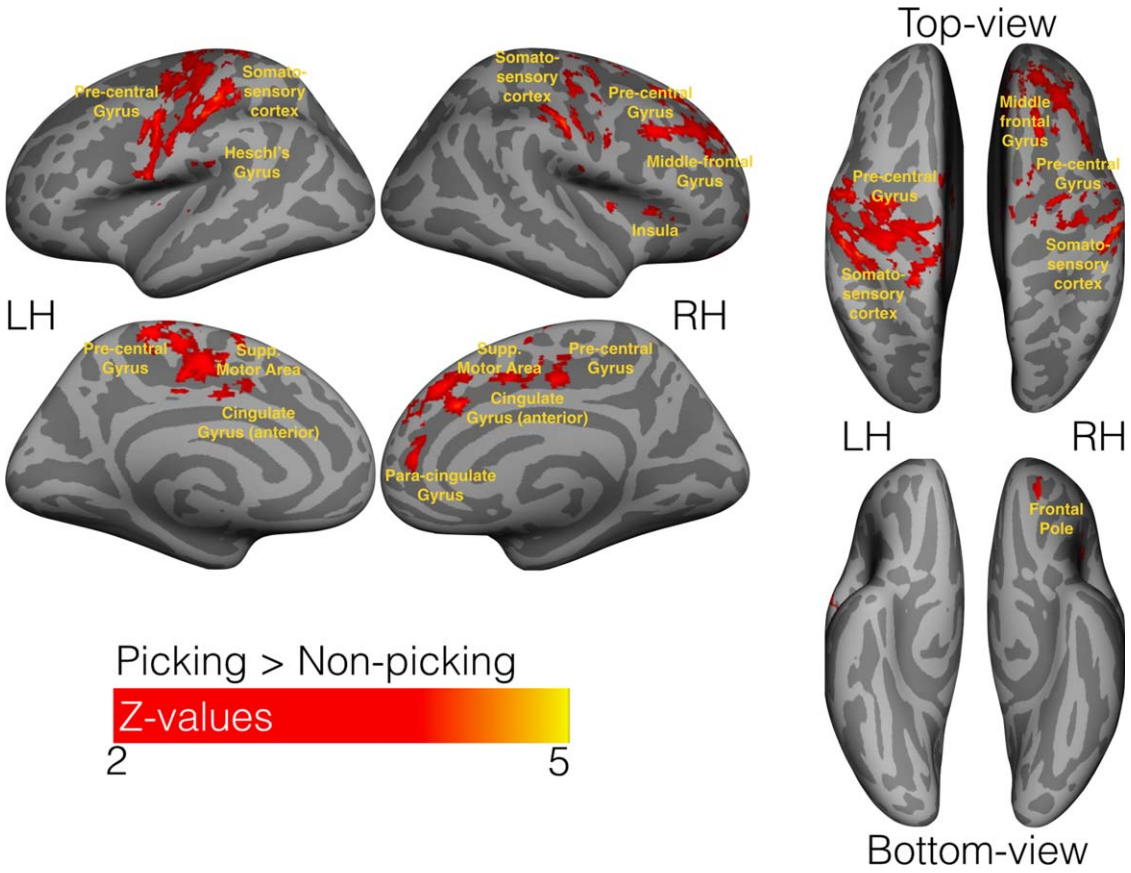

Figure 1.

Random effects analysis of the skin-picking > nonpicking contrast for 10 participants with PWS. A cluster correction of 1.96 was used. None of the clusters reached significance in the reverse contrast. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of interoceptive circuitry occurs during skin-picking episodes in participants with PWS.

To minimize the effects of motion artifact on our data, we selected runs with limited in-scanner motion and also used sophisticated motor correction procedures. Overall, we found that motion related artifact was not significant with the mean relative head displacement being 0.47 mm (SD = 0.41) across all participants. The results from this study, therefore, demonstrate the feasibility of examining the neural correlates of skin-picking behaviors in PWS with fMRI.

Within our correlational findings, we found a significant negative relationship between skin-picking severity (as demonstrated by the SIT Scale NI) and BOLD activation within the right insula. These findings are consistent with those from hunger/satiety studies in PWS in which abnormal insula activation has been shown to be directly related to pathological eating behaviors in PWS [Ogura et al., 2013] and, specifically, that a delay in insula activation is associated with abnormal satiety in PWS [Shapira et al., 2005]. Thus, pathological behaviors displayed in those with PWS, such as skin picking and overeating appear to be linked to insula function.

Our neuroimaging results, particularly the relationship between insula activation and SIB severity, suggest that skin-picking behaviors in PWS may be reinforced by interoceptive consequences, supporting Lovaas's et al. theory of perceptual reinforcement [Lovaas et al., 1987]. These authors suggest that repetitive behaviors such as skin picking are operant behaviors, shaped and maintained by the interoceptive and exteroceptive consequences that are automatically produced. Given that individuals with PWS demonstrate evidence of interoceptive deficits—such as difficulties regulating one's food intake and possible pain threshold disturbances—it is likely that the increased stimulation provided by skin-picking behaviors could be rewarding as these behaviors may assist in optimally regulating one's internal state.

Our study is similar to other studies that have examined itch and scratching behaviors using fMRI [Papoiu et al.,

TABLE III. Local maxima locations (in Talairach space) and corresponding Brodmann areas within each cluster for the skin-picking > nonpicking contrast.

	Cluster size	Peak Z	Side	BA	Coordinates		
					x	*y*	*z*
Picking > nonpicking							
Inferior parietal lobule[a]	6,661	4.01	L	40	−47	−30	46
Postcentral gyrus	—	3.59	R	3	48	−21	37
Postcentral gyrus	—	3.56	L	2	−49	−26	39
Paracentral lobule	—	3.47	L	31	−1	−11	46
Medial frontal gyrus	—	3.46	L	6	−1	−8	46
Anterior cingulate	2,727	3.40	R	32	18	29	14
Cingulate gyrus	—	3.39	R	32	14	22	34
Medial frontal gyrus	—	3.35	R	8	8	29	34
Medial frontal gyrus	—	3.25	R	8	25	12	33
Cingulate gyrus	—	3.23	R	32	14	21	45

Note. BA = Brodmann Area. L = left; B = Bilateral. In regions with more than one cluster of activation, coordinates are listed for the cluster with highest activation.

[a]Number of voxels was listed only for main clusters only; Number of voxels and coordinates were not listed for local maxima regions within clusters.

2013; Vierow et al., 2009; Yosipovitch et al., 2008]. Specifically, our findings are consistent with those by Vierow et al. who found that bilateral premotor and somatosensory regions were activated in typically developing adult participants during itch and scratching behaviors. Our findings are also consistent with other studies of scratching behaviors that have demonstrated that somatosensory and motor cortices were simultaneously implicated [Mochizuki et al., 2014; Papoiu et al., 2013; Yosipovitch et al., 2008].

Our study results are also comparable to those of Bohlhalter and coworkers who used fMRI to examine the neural correlates of spontaneous tic behaviors in patients with Tourette syndrome [Bohlhalter et al., 2006]. These authors found that premotor and somatosensory regions were activated during tic behaviors. Our findings, together with those of Bohlhalter et al., suggest that skin picking, tics, and active scratching behaviors are associated with a "need to move" [Bohlhalter et al., 2006].

Within left precentral/primary motor regions, we also found a significant negative relationship between skin-picking severity (as demonstrated by the SIT Scale NI) and BOLD activation. Like interoceptive processing within the insula, these results suggest that skin-picking behaviors may increase activation within motor regions, and thus, skin-picking behaviors may activate internal interoceptive sensory regions and also motor regions.

Strengths and Limitations

This study was conducted to better understand the brain mechanisms underlying skin-picking behaviors in PWS and to demonstrate the feasibility of examining neural mechanisms underlying skin-picking behaviors in PWS. To our knowledge, this is the first study to examine skin-picking behaviors in patients with PWS using fMRI. By allowing our subjects to freely engage in skin picking in the MRI scanner, we were able to naturally capture spontaneous skin-picking episodes. We also used state of the

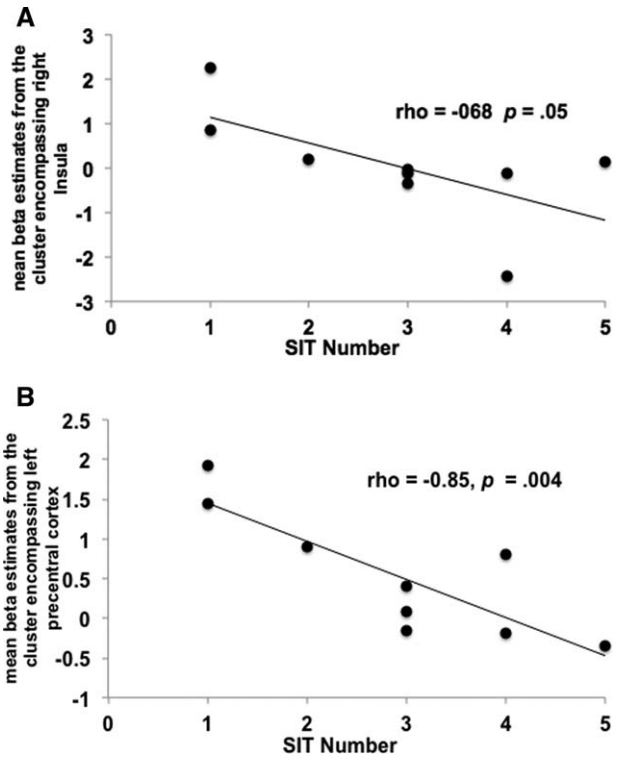

Figure 2.
Correlation between the SIT NI and the mean parameter estimate obtained from the skin picking > nonpicking contrast in the (**a**) right insula and (**b**) left precentral cortex.

art motion correction procedures during analyses to additionally account for skin picking related motion. By rating skin-picking behaviors, we attempted to directly measure the brain's response associated with the initiation of skin-picking behaviors.

This study also has several limitations that should be considered. First, we were unable to compare patients with PWS to other individuals without PWS. As a result, we do not know whether the brain processes underlying skin-picking behaviors observed throughout this study are specific to PWS. We found, however, that BOLD activation within specific regions (insula and precentral/primary motor regions) is directly associated with skin-picking severity. Second, given that subjects were allowed to freely engage in skin picking in the scanner, it was problematic to ensure that equal amounts of picking and nonpicking blocks occurred during the scan across participants. During each scanner session, participants engaged in skin picking for an average of 57% of the time with the average length of the participants' skin-picking episodes being 33.6 s. Third, the fact that participants with PWS were given permission to engage in skin picking during the scan, without the threat of admonishment, may also have influenced the results. It is possible, for example, that brain activation in the context of the imaging experiment may have been different from the brain activation that typically occurs when skin picking occurs in private, which is often the case for individuals with PWS. Lastly, in addition to assessing brain activity during episodes of active skin picking, we planned to examine brain activity immediately before skin-picking episodes. Unfortunately, we were unable to examine periods immediately prior to skin-picking onset as the interepisode durations were highly variable (see Table II) and the modeled hemodynamic response function would, therefore, have overlapped with the next skin-picking onset.

In regards to further studying itch in PWS, studies should examine the effect of histamines or allergens on blood flow changes within the skin. These studies can help us determine whether skin-picking behaviors are initially triggered by exteroceptive skin stimuli. Itch studies in PWS should also examine how the gastric releasing protein within the dorsal horn contributes to skin-picking symptoms in PWS. Examining this protein may help us conclude whether skin-picking behaviors in PWS occur in response to itch dysfunction at the receptor/cellular/chemical level.

Studies should also additionally examine whether skin-picking behaviors are trigged by situations lacking in environmental exteroceptive stimuli. If this were the case, the function of skin-picking behaviors may be to stimulate the insula and other regions involved in interoceptive processing and increase stimuli required to balance one's internal homeostasis during situations that lack external stimulation. In our previous study [Hall et al., 2014], we found that skin picking primarily occurred during the absence of external stimulation (i.e., when the participants were left alone with nothing to do). In a related sense, studies should also examine whether skin-picking behaviors occur in response to distorted homeostatic error monitoring [which results from abnormal pain processing; Handwerker and Schmelz, 2009; LaMotte et al., 2014; Leknes et al., 2007] or whether global brain deficits impacting the interoceptive neural networks influence multiple interoceptive senses in PWS.

The results of this study imply potential treatment options for those with PWS. It may be beneficial to teach those with PWS more adaptive ways to stimulate and regulate one's internal state than engaging in skin-picking and overeating behaviors. Additionally, medications that stimulate and regulate one's internal state may be helpful to either use or develop for use in PWS. Also, it may be helpful to educate those with PWS and their families on the neurobiology underlying skin-picking and overeating behaviors in PWS. Patients should be taught that they may not be able to depend on pain or interoceptive cues when regulating internal homeostatic functioning. Rather, it may be beneficial to teach those with PWS how to use exteroceptive stimuli to regulate one's internal state. For example, it may be appropriate for those with PWS to wear gloves in unstimulating situations and or to have access to toys that they can fidget with as an alternative option to skin-picking behaviors. Additionally, those with PWS should be encouraged to eat during preset meal times and also to eat predetermined food servings instead of relying on hunger and satiety signals to determine when to start and stop eating. Future studies should examine the efficacy of such behavioral techniques and/or medications in improving regulatory behaviors in those with PWS.

CONCLUSIONS

The results of this study provide important information about the neural activation underlying skin-picking behaviors in those with PWS. Our results suggest that interoceptive disturbances may directly contribute to skin-picking symptom severity in PWS and should be further studied. Examining interoception in PWS may provide valuable information about the genetics underlying interoceptive disturbances detected across neurogenetic and psychiatric disorders. In addition, this study may help us better understand why abnormal behaviors occur in those with interoceptive disturbances and inform potential treatment options for these behaviors.

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