

White Matter Abnormalities in Skin Picking Disorder: A Diffusion Tensor Imaging Study

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Skin picking disorder (SPD) is characterized by the repetitive and compulsive picking of skin, resulting in tissue damage. Neurocognitive findings in SPD implicate difficulty with response inhibition (suppression of pre-potent motor responses). This function is dependent on the integrity of the right frontal gyrus and the anterior cingulate cortices, and white-matter tracts connecting such neural nodes. It was hypothesized that SPD would be associated with reduced fractional anisotropy in regions implicated in top-down response suppression, particularly white-matter tracts in proximity of the bilateral anterior cingulate and right frontal (especially orbitofrontal and inferior frontal) cortices. 13-subjects meeting proposed SPD criteria for DSM-5 free from other current psychiatric comorbidities, and 12 healthy comparison subjects underwent MRI with a 3-T system. Between-group comparisons of imaging data underwent voxelwise analysis with permutation modeling and cluster correction. Fractional anisotropy (measured using diffusion tensor imaging) was the primary outcome measure. Subjects with SPD exhibited significantly reduced fractional anisotropy in tracts distributed bilaterally, which included the anterior cingulate cortices. Fractional anisotropy did not correlate significantly with SPD disease severity, or depressive or anxiety scores. These findings implicate disorganization of white-matter tracts involved in motor generation and suppression in the pathophysiology of SPD, findings remarkably similar to those previously reported in trichotillomania. This study adds considerable support to the notion that—in addition to the phenomenological and comorbid overlap between SPD and trichotillomania—these disorders likely share overlapping neurobiology.

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INTRODUCTION

Skin picking disorder (SPD; also known as pathological skin picking, neurotic/psychogenic excoriation, and dermatillomania) is characterized by the repetitive and compulsive picking of skin, which causes tissue damage (Arnold *et al*, 2001; Grant *et al*, 2012). Although SPD has an estimated prevalence rate ranging from 1.4 to 4.2% (Keuthen *et al*, 2010; Odlaug *et al*, 2012), it is not explicitly listed in the current Diagnostic and Statistical Manual (DSM-IV-TR) (American Psychiatric Association, 2000). SPD is likely to be included in the DSM-V with the following criteria: (1) recurrent skin picking resulting in skin lesions; (2) repeated attempts to decrease or stop skin picking; (3) skin picking causes clinically significant distress or impairment in social,

occupational, or other important areas of functioning; (4) skin picking is not due to the direct physiological effects of a substance (eg, cocaine) or a general medical condition (eg, scabies); and (5) skin picking is not restricted to the symptoms of another mental disorder (eg, skin picking due to fixed beliefs about skin infestation in delusional disorder, preoccupation with appearance in body-dysmorphic disorder) (www.DSM5.org).

SPD typically begins in adolescence and is thought to be more common in women (Odlaug and Grant, 2012; Tucker *et al*, 2011). Individuals with SPD may pick at any bodily site, but most frequently pick the face, arms and legs (Flessner and Woods, 2006; Odlaug and Grant, 2012). The disorder subtends considerable functional impairment—a survey of 760 sufferers found that ~48% picked at their skin for over 1 h each day, 63% avoided socializing due to picking, 58% would not go out into public due to their picking, and one-third reported missing school or work frequently due to picking (Tucker *et al*, 2011). There are also important medical sequelae of SPD, including infections, lesions, scarring, and serious physical disfigurement (Odlaug and Grant, 2008a). In the most severe cases,

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individuals may be at heightened risk of mortality and warrant neurosurgical intervention (Kondziolka and Hudak, 2008).

The nosological status of SPD and its relationship with other axis I disorders remains unclear. Individuals with SPD report high rates of co-occurring trichotillomania, and first-degree relatives of patients with SPD report high rates of grooming behaviors, including trichotillomania and SPD (Odlaug and Grant, 2008a,b; Wilhelm *et al*, 1999; Neziroglu *et al*, 2008). Given this overlapping familiarity between SPD and trichotillomania, and that these conditions are associated with pathological habits that are difficult to suppress, it has been suggested that SPD can be viewed as a pathological grooming disorder alongside trichotillomania (Stein *et al*, 1994; Feusner *et al*, 2009; Beinvenu *et al*, 2012).

One critical means of attempting to understand SPD and its relationship with other disorders is by identifying neural circuitry involved in the pathophysiology. Techniques grounded in the neurosciences, such as brain imaging, have shown considerable success in elucidating the neurobiology of other putative 'habit disorders', such as obsessive-compulsive disorder (OCD) (eg, see Chamberlain and Menzies, 2009). In stark contrast, there exist no prior published imaging studies of patients with SPD, although neural abnormalities may be predicted for several reasons. One of the few cognitive studies to date in SPD identified impaired performance on a task quantifying the ability to suppress impulsive premature motor responses—the stop-signal test (SST) (Odlaug *et al*, 2010). Prior data from functional imaging and studies in patients with focal-neural damage show that stop-signal response inhibition is dependent on the integrity of a neural network including the right inferior frontal gyrus and the anterior cingulate cortices (eg, Sharp *et al*, 2010). Additionally, individuals with trichotillomania—a disorder with considerable phenomenological and comorbid overlap with SPD—demonstrated abnormally reduced integrity of white-matter tracts connecting nodes, such as the anterior cingulate and frontal cortices, compared to healthy controls (Chamberlain *et al*, 2010).

The aim of this study was to assess the integrity of white-matter tracts in subjects with SPD compared with healthy control subjects. In particular, we sought to conduct an analysis across all white-matter tracts within the brain using diffusion tensor imaging (DTI) alongside recently validated and statistically powerful methods of permutation cluster analysis to ensure stringent corrections for multiple comparisons (Suckling *et al*, 2006). It was hypothesized that SPD would be associated with reduced fractional anisotropy (FA), thought to be characteristic of disorganized and/or damaged white-matter tracts (Beaulieu, 2002), in regions implicated in top-down response suppression and in trichotillomania (Chamberlain *et al*, 2010). In particular, we predicted reduced FA of white-matter tracts in proximity of the bilateral anterior cingulate and predominantly right frontal (especially orbitofrontal and inferior frontal) cortices. Furthermore, we predicted that areas of reduced FA in SPD would overlap descriptively with those reported previously in patients with trichotillomania.

MATERIALS AND METHODS

Subjects

Men and women aged 18–49 years with a primary diagnosis of SPD based on proposed criteria for DSM-5 were recruited by newspaper and poster advertisements. Subjects were recruited from November 2010 through May 2012.

Inclusion criteria included: (1) subjects met all five proposed DSM-5 criteria for SPD (see introduction) for at least the past 12 months, (2) a minimum score of >16 on the Yale Brown Obsessive Compulsive Scale modified for neurotic excoriation (NE-YBOCS), and (3) picking behavior occurred daily for at least 30 min.

Exclusion criteria in those with SPD comprised: (1) unstable medical illness or clinically significant abnormalities on physical examination; (2) current pregnancy; (3) lifetime history of bipolar disorder type I or II, dementia, or any psychotic disorder; (4) any current (past 12 months) DSM-IV axis I disorder, including nicotine dependence and impulse control disorders; (5) initiation of psychotherapy or pharmacotherapy within 3 months prior to study entry, or any changes to pre-established treatment doses in the 3 months prior to study entry; (6) history of head injury or neurologic disorders; and (7) any known contraindications to MRI.

The institutional review board for the University of Minnesota approved the study. After complete description of the study, and opportunities to ask any questions, all subjects provided written informed consent. This study was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Control subjects, matched for age and gender, were recruited from the local community using media advertisements on the basis of freedom from any lifetime or current axis I disorders according to the Structured Clinical Interview for DSM-IV (SCID) (First *et al*, 1995). Exclusion criteria for controls matched those for SPD subjects.

Assessments

Lifetime and current psychiatric comorbidity was assessed using the Structured Clinical Interview for DSM-IV (First *et al*, 1995). SPD severity was assessed using the Yale Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation (NE-YBOCS) (Arnold *et al*, 1999; Grant *et al*, 2007) and the Clinical Global Impressions—Severity (CGI) Scale (Guy, 1976). Social functioning, anxiety, and depressive symptoms were assessed using the Sheehan Disability Scale (SDS) (Sheehan, 1983), Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

Neuroimaging and Analysis

SPD subjects and controls were compared on demographic characteristics using independent sample *t*-tests, with significance defined as $P < 0.05$, uncorrected.

Imaging data were acquired using a 3-T system at the University of Minnesota, USA. Diffusion-weighted imaging data were obtained (25 directions) with slice thickness of 4 mm, temporal resolution of 12 s, echo time of 93 ms,

matrix size of 128×128 , field of view of $30 \times 24 \text{ cm}^2$, and B-value of 1000 s/mm^2 . One volume without diffusion weighting ($b = 0$) was also acquired. To provide a reference for normalization, axial three-dimensional T1-weighted images were obtained using a spoiled-gradient recall sequence with slice thickness of 2 mm, temporal resolution of 33 ms, echo time of 3 ms, field of view of 24 cm, flip angle of 40° , and matrix size of 256×256 .

Voxelwise statistical analysis of the imaging data was carried out using TBSS (Tract-Based Spatial Statistics), which is part of the FSL software package (Smith *et al*, 2004, 2006; Woolrich *et al*, 2009). FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then extracting brain data using BET (Smith, 2002). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson *et al*, 2007)—this uses a b-spline representation of the registration warp field (Rueckert *et al*, 1999). The mean FA image was then created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and fed forward into voxelwise cross-subject statistics. Cross-group contrasts were generated using permutation modeling with the FSL Randomise toolbox (Nichols and Holmes, 2002). The resultant statistical images were rendered with cluster correction (Bullmore *et al*, 1999) for the entire search volume using threshold-free-cluster enhancement at $P < 0.05$. In order to explore possible structure–function relationships, we also conducted correlation analyses (Spearman's r) between mean FA for any clusters of white matter exhibiting significant group differences and (i) NE-YBOCS (SPD cases), (ii) HARS (in the whole sample, and in SPD cases

alone), and (iii) HDRS (in the whole sample, and in SPD cases alone).

RESULTS

Thirteen subjects (mean age 26.4, SD = 5.5) with SPD and 12 age-matched control subjects (mean age 26.0, SD = 6.4) met the inclusion criteria and underwent imaging. No clinically significant MRI structural abnormalities were identified in any subjects.

Demographic characteristics of the included sample are presented in Table 1, where it can be seen that the groups did not differ significantly in terms of age, sex, or handedness. The SPD group showed moderate to severe SPD severity (NE-YBOCS scores). Depression and anxiety scores were significantly higher in the SPD sample compared to healthy controls, as expected. Mean scores were well beneath threshold for clinically significant anxiety/depression, consistent with exclusionary criteria. Two subjects were currently taking psychotropic medications, both of whom were taking stable doses for over a year: One subject was taking bupropion (450 mg/day), venlafaxine (225 mg/day), and trazodone (100 mg/prn), whereas the other was taking lamotrigine (300 mg/day), venlafaxine (375 mg/day), and trazodone (100 mg/prn). No one was receiving cognitive behavioral therapy for SPD. Findings were unchanged in an analysis restricted to the unmedicated subjects. In the SPD group, four subjects reported lifetime history of major depressive disorder, one of whom also reported lifetime history of generalized anxiety disorder. All subjects were free from past year axis I disorders at the time of study participation (except for SPD in the clinical group), per inclusion/exclusion criteria.

Table 1 Baseline Comparison of Skin Picking Disorder Subjects and Controls

Variable ^a	Baseline		Test ^b	df	P-value
	SPD (n = 13)	Controls (n = 12)			
Age, years	26.4 (5.5)	26.0 (6.4)	0.161	23	0.875
Sex, female, n (%)	13 (100)	11 (91.6)	f	1	0.479
White/Caucasian, n (%)	12 (92.3)	10 (83.3)	f	1	0.593
Single, n (%)	10 (76.9)	10 (83.3)	f	1	1
Education, n (%)					
Less than a college degree	4 (33.3)	3 (25)	f	1	1
College degree or higher	8 (66.7)	9 (75)			
Right handedness, n (%)	11 (84.6)	11 (91.6)	f	1	1
Age of onset, years	10.1 (3.5)				
Any lifetime psychiatric comorbidity, n (%)	4 (33.3)				
NE-YBOCS total score	21.7 (4.6)				
Clinical Global Impressions—Severity Scale	4.4 (0.7)				
Sheehan Disability Scale	13.8 (6.1)				
Hamilton Depression Rating Scale	4.8 (3.3)	0.5 (1.4)	4.079	23	<0.001
Hamilton Anxiety Rating Scale	4.7 (3.5)	0.4 (0.8)	4.214	23	<0.001

NE-YBOCS = Yale Brown obsessive compulsive scale modified for neurotic excoriation.

^aAll variables are mean (\pm SD) (range) unless otherwise indicated.

^bt-test unless otherwise indicated (f = Fisher's Exact test).

Table 2 Regions of Significantly Reduced FA in SPD vs Controls, and their Anatomical Extent

MNI co-ordinates			FSL atlas labels	
X	Y	Z	JHU ICBM-DTI white-matter labels	JHU white-matter tractography atlas
<i>Right</i>				
Extending from (medial)				
0	26	11	Genu of corpus callosum	Forceps minor/cingulate gyrus
Anterior towards				
19	42	0	Anterior corona radiata	Forceps minor/uncinate fasciculus
Down to				
17	30	− 10	Anterior corona radiata	Inferior fronto-occipital fasciculus/uncinate fasciculus/anterior thalamic radiation
Up to				
16	20	26	Anterior corona radiata	Cingulate gyrus
<i>Left</i>				
Extending from (medial)				
− 11	33	9	Genu of corpus callosum	Forceps minor/cingulate gyrus
Anterior towards				
− 30	36	3	Anterior corona radiata	Inferior fronto-occipital fasciculus
Down to				
− 16	31	− 10	Anterior corona radiata	Inferior fronto-occipital fasciculus/uncinate fasciculus/anterior thalamic radiation
Up to				
− 9	19	26	Cingulate gyrus	Cingulate gyrus
Also				
− 37	− 45	4	Posterior thalamic radiation	Inferior fronto-occipital fasciculus/inferior longitudinal fasciculus

Analysis of DTI data identified multiple white-matter regions with significantly reduced FA in patients with SPD *vs* controls. These abnormal regions involved distributed tracts (Table 2), maximal in the region of the bilateral anterior cingulate cortices (exemplified in Figure 1), but also including white matter in proximity of the left temporoparietal junction. No significant correlations were found between mean FA in this cluster and NE-YBOCS in SPD, nor between mean FA in this cluster and anxiety/depression scores, either in the whole sample or in patients considered as a group (all $P > 0.10$, uncorrected).

DISCUSSION

Even with a long history in the medical literature, the neurobiology of SPD has received little research attention. To our knowledge, this is the first neuroimaging study of individuals with SPD. The key finding was that SPD was associated with reduced integrity of distributed white-matter tracts connecting the anterior cingulate cortices to other neural nodes bilaterally. Patients were free from current axis I comorbidities and the majority were also free from medications ($n = 11$, 84.6%). The FA abnormalities in SPD appeared unrelated to the extent of disease severity as indexed by NE-YBOCS scores.

The current data implicate disconnectivity in white-matter tracts connecting neural regions involved in motor generation and suppression. Although caution is warranted when comparing imaging findings across studies, the regions of white matter exhibiting abnormally reduced FA seen here in SPD show remarkable overlap with those previously identified as abnormal in trichotillomania (Figure 2) (Chamberlain *et al*, 2010). These findings add considerable support to the notion that—in addition to the phenomenological and comorbid overlap between SPD and trichotillomania—these disorders likely share overlapping neurobiology.

Individuals with SPD report repetitive picking, sometimes for several hours at a time, with an inability to stop the behavior despite ongoing damage to the skin. A significant amount of imaging evidence in humans suggests that the orbitofrontal cortices and anterior cingulate cortices, working with other neural regions such as the right inferior frontal gyrus and the pre-supplementary motor area, have crucial roles in conditioned responses and response suppression (Rubia *et al*, 2003; Chambers *et al*, 2009). Thus, these findings are consistent with cognitive assessments of individuals with SPD, wherein individuals with SPD exhibited impairment on the SST, a test of motor inhibition (Odlaug *et al*, 2010; Grant *et al*, 2011).

The interactions between the anterior cingulate cortices and the orbitofrontal cortices are also believed to be

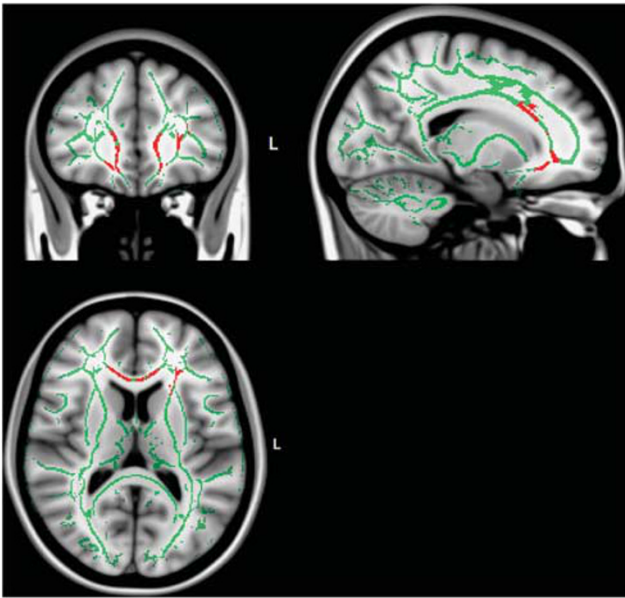


Figure 1 Diffusion tensor imaging (DTI) results; example brain slices highlighting regions of abnormally reduced FA in patients vs controls (shown in red) in proximity to the bilateral anterior cingulate cortices. In green, skeleton of DTI tracts used to provide mask for analysis.

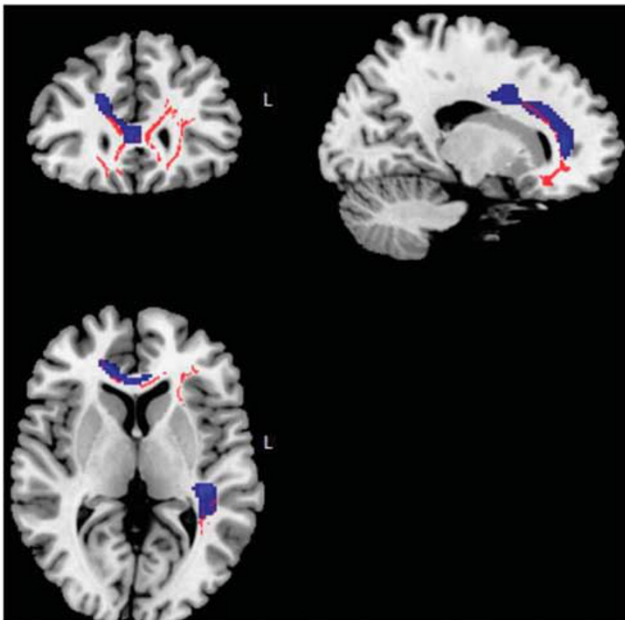


Figure 2 Representative brain slices exemplifying anatomic overlap in the regions of abnormally reduced FA reported here in SPD vs controls (red) to those previously identified, using non TBSS, in trichotillomania vs controls (blue). Overlap was particularly pronounced for white-matter tracts implicating predominantly right-sided anterior cingulate and left temporal cortices.

important when error feedback suggests a change, or reversal in choice is required (Bush *et al*, 2003; Ridderinkhof *et al*, 2004; Murray *et al*, 2007). Clinically, SPD is characterized by picking at areas of the skin that seem to be ‘wrong’ with the rest of the skin (eg, bumps, red

patches, acne, or blemishes). The person continues to pick, always being aware that they are making the skin worse, but they report a distorted belief that they might make the skin better. This inability to make different choices based on error assessment may explain in part why so few individuals with SPD (16.1%) report improvement in their picking even when seeking treatment (Tucker *et al*, 2011).

Structural brain abnormalities reported here are interesting in light of animal models, particularly the *hoxb8* gene-knockout mouse (Greer and Capecchi, 2002). Mice with the *hoxb8*-knockout genetic mutation groom excessively, resulting in hair loss and open skin lesions. Within the mouse brain, *hoxb8* is expressed in microglia, which appear to migrate from bone marrow to brain (Chen *et al*, 2010; for discussion see Hyman, 2010). Microglia expressing *hoxb8* have been found in the cerebral cortex, striatum, olfactory bulb, and brainstem. The mechanism by which *hoxb8*-expressing microglia influence grooming behavior in animals is unclear, perhaps stemming from paracrine effects rather than direct interactions with neurons or synaptic connections (Hyman, 2010). Though caution is warranted when comparing brain findings across species, as homology of brain regions cannot be assumed, both the *hoxb8* animal model and the current DTI findings in humans implicate frontostriatal circuitry in pathological grooming.

This study has several positive features, notably that it is the first imaging study in SPD, the first to use DTI, its use of advanced and statistically powerful permutation-cluster analysis, and the subjects with SPD were free from axis I comorbidities. Several limitations, however, should be considered. As we recruited from media advertisements, there is the possibility of selection bias. We do not yet know whether these findings in moderately ill people recruited via advertisements with no current comorbidities generalize to SPD more broadly. Although people with SPD were free from anxiety and depressive disorders, and scored well beneath threshold for clinically significant mood/anxiety symptoms, their HARS/HDRS scores were nonetheless statistically higher than controls, as expected. We could find no evidence for a significant relationship between the FA abnormalities and extent of SPD severity (NE-YBOCS), or subclinical depressive/anxiety scores (HARS/HDRS). It should be noted that the study may have been underpowered to detect such relationships. However, a previous study in trichotillomania using DTI likewise did not find such significant severity-FA relationships (Chamberlain *et al*, 2010). It may be that these abnormalities reflect predisposing or candidate ‘vulnerability’ markers, which occur in people at-risk of developing SPD without symptoms, that is, predate the onset of symptoms. Future work could explore this issue by enrolling not only people with SPD but also their unaffected first-degree relatives, and consider whether they too manifest such abnormalities. Finally, in terms of limitations, we did not have access to subjects’ medical records; therefore, our strategy to elicit current axis I disorders and history of axis I disorders was based on the SCID and self-completed questionnaires, which may have hindered the reliability to detect comorbidities in the past and present. Also, the study was neither designed nor powered to assess influences of lifetime comorbidities on FA measures.

In summary, our results provide preliminary support for the hypothesis that neural circuits involved in the generation and suppression of motor responses are implicated in repetitive picking behavior. Future work should use diffusion tensor imaging in conjunction with functional imaging to explore the relationship between white-matter tract disorganization and dysfunction of particular nodes within the networks responsible for habit suppression.

DISCLOSURE

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