Striatal abnormalities in trichotillomania: A multi-site MRI analysis

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\textbf{ABSTRACT}

Trichotillomania (hair-pulling disorder) is characterized by the repetitive pulling out of one's own hair, and is classified as an Obsessive-Compulsive Related Disorder. Abnormalities of the ventral and dorsal striatum have been implicated in disease models of trichotillomania, based on translational research, but direct evidence is lacking. The aim of this study was to elucidate subcortical morphometric abnormalities, including localized curvature changes, in trichotillomania. De-identified MRI scans were pooled by contacting authors of previous peer-reviewed studies that examined brain structure in adult patients with trichotillomania, following an extensive literature search. Group differences on subcortical volumes of interest were explored (t-tests) and localized differences in subcortical structure morphology were quantified using permutation testing. The pooled sample comprised \( N = 68 \) individuals with trichotillomania and \( N = 41 \) healthy controls. Groups were well-matched in terms of age, gender, and educational levels. Significant volumetric reductions were found in trichotillomania patients versus controls in right amygdala and left putamen. Localized shape deformities were found in bilateral nucleus accumbens, bilateral amygdala, right caudate and right putamen. Structural abnormalities of subcortical regions involved in affect regulation, inhibitory control, and habit generation, play a key role in the pathophysiology of trichotillomania. Trichotillomania may constitute a useful model through which to better understand other compulsive symptoms. These findings may account for why certain medications appear effective for trichotillomania, namely those modulating subcortical dopamine and glutamatergic function. Future work should study the state versus trait nature of these changes, and the impact of treatment.

1. Introduction

Trichotillomania, also known as hair-pulling disorder, is characterized by the repetitive pulling out of one's own hair, leading to significant functional impairment (APA, 2013). The condition has lifetime prevalence of 0.5–1% based on surveys, yet is often hidden, undiagnosed and untreated (Grant et al., 2016; Woods et al., 2006). Trichotillomania has peak age of onset in adolescence, is more common in women than in men, and is currently classified as an Obsessive-Compulsive Related Disorder (Grant and Chamberlain, 2016). However, in contrast to the repetitive compulsive acts observed in obsessive-compulsive disorder (OCD), repetitive behaviors in trichotillomania are not generally driven by intrusive thoughts. As such, and in view of the recent development of animal models with good validity (Grant et al., 2007b; Greer and Capanedi, 2002; Hyman, 2007), trichotillomania constitutes a key model for better understanding compulsive symptoms more generally. However, surprisingly little is known about the neurobiological basis of this disorder in humans (Christenson et al., 1993; Cohen et al., 1995; Mansueto et al., 2007; Odlug and Grant, 2010).

Reviewing available clinical and imaging studies of trichotillomania, previous work suggested an “ABC” model of trichotillomania emphasizing the dysfunction of pathways involved in affect regulation, behavioral control, and cognition (Stein et al., 2006). This approach implicates, in turn, the frontal cortices (serving to regulate impulses and habits), the amygdala (involved in emotional processing) (Canli et al., 2005), and the striatum (playing key roles in reward processing and motor outflow) (Ahmari et al., 2013; Knutson et al., 2001). In keeping
with this, studies have found that trichotillomania is associated with impairment on response inhibition tests (Chamberlain et al., 2006; Odlaug et al., 2014), and phenomenological studies have found relationships between emotional states (dysphoria, anxiety) and the severity of the hair-pulling symptoms (Grant et al., 2017).

Neuroimaging constitutes a core modality through which to evaluate implicated neural regions in patients with trichotillomania. Structural imaging studies comparing patients with trichotillomania to controls have yielded mixed results with regards to the basal ganglia. One study found no volumetric changes in the caudate (Stein et al., 1997), one found no difference in the global basal ganglia (Roos et al., 2015), one found reduced left putamen volumes (O’Sullivan et al., 1997), and another found excess grey matter density in left putamen and amygdala (Chamberlain et al., 2008). Due to the relatively limited research scrutiny of this disorder, and limited funding, imaging studies have typically involved relatively small sample sizes. Small sample sizes result in limited statistical power and elevate the risk of false positive findings (Button et al., 2013). Subcortical structures are difficult to visualize due to poor and variable signal intensity (as compared to cortex) (Patenaude et al., 2011) and several mainstream imaging analysis pipelines were designed for analysis of cortex rather than subcortical regions (Dale et al., 1999). More recent pipelines enable the sensitive measurement not only of volumes of subcortical structures, but also of local differences in deformations of shape across groups; the latter has the advantage of not relying on arbitrary smoothing extent or tissue classification (Patenaude et al., 2011).

Therefore, the current study pooled together raw MRI scans from all available peer-reviewed case-control studies of trichotillomania, and evaluated the volume and morphology of select subcortical structures. Software pipelines, including “vertex analysis” from FMRIB’s Software Library (FSL) were used, these being designed specifically for the sensitive measurement of subcortical structures (Patenaude et al., 2011). We hypothesized that trichotillomania would be associated with volumetric and morphometric abnormalities of the caudate, putamen, nucleus accumbens, and amygdala (Stein et al., 2006).

2. Material and methods

2.1. Data collection of participants

Conventional cortical data for the current sample were reported previously and the MRI dataset obtained here was the same as that used by the previous study (Chamberlain et al., 2017). In brief, all structural MRI studies regarding trichotillomania were identified via PubMed in February 2017. We contacted the authors of these publications and invited them to contribute de-identified MRI scans from published studies, subject to original participating procedures having appropriate consent and Institutional Board Approvals. De-identified T1-weighted MRI images and demographic data were shared for patients and controls. Demographic data consisted of age, gender, level of education, medication status, and severity of illness measured with the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) (Keuthen et al., 2007), which is a self-administered questionnaire assessing severity of trichotillomania. We excluded trichotillomania patients who were taking psychotropic medication at the time of study participation, to avoid potentially confounding effects of medication on brain structure (McDonald, 2015). This applied to six patients.

2.2. Data analysis

Group differences in demographic data were explored with independent sample t-tests (\(p < 0.05\), two-tailed, uncorrected) and chi-square tests (\(p < 0.05\)), using JMP Pro.

Imaging pre-processing and data extractions were undertaken on the University of Chicago Midway computing system. The T1-weighted images of each subject were preprocessed. They were automatically bias-field corrected and non-linearly registered to the MNI 152 standard space. We employed FMRIB’s Integrated Registration and Segmentation Tool (FIRST) implemented in FSL 5.0.9 to automatically segment subcortical structures (Patenaude et al., 2011). Segmentation was based on shape models with structural boundaries obtained from 336 manually segmented images, and resulted in a deformable surface mesh of each subcortical structure consisting of vertices. The meshes were re-constructed and filled in MNI space and boundary correction was applied. Then, the segmented images were transformed into original space. All segmented images were visually checked for errors in registration and segmentation and the images of 2 trichotillomania patients were discarded due to poor quality in segmentation.

2.2.2. Vertex analysis

Vertex analysis, implemented in FIRST, (FSL), was employed to compare the shapes of the subcortical structures between groups (Patenaude et al., 2011). The vertex locations of each participant were projected onto the surface normal of the average shape template of the 336 training subjects provided by FSL, and the perpendicular distance from the average surface was calculated. Negative value of the vertex represented deformation in the inward direction and positive value of a vertex indicated deformation in the outward direction. These values were compared between groups using ‘Randomise’, a permutation-based non-parametric testing method implemented in FSL with 5000 iterations (Winkler et al., 2014). The statistical images were produced with Threshold-Free Cluster Enhancement (TFCE) for multiple comparisons (Smith and Nichols, 2009), in which threshold was set at \(p < 0.05\).

3. Results

3.1. Demographics

The final study sample comprised 68 individuals with trichotillomania and 41 healthy controls. The mean total Massachusetts General Hospital Hair Pulling Scale severity score in the trichotillomania group was 15.6 (standard deviation 4.7), consistent with, on average, mild-moderate illness. There were no significant differences in age, gender, education level, total grey and white matter volumes, or total intracranial volume, between the groups (Table 1).

3.2. Volumetric analysis

Absolute volumetric data of subcortical grey matter regions were listed and results of group comparisons are shown in Table 2. With
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