Grey matter abnormalities in trichotillomania: morphometric magnetic resonance imaging study

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Background
Trichotillomania (repetitive hair-pulling) is an Axis I psychiatric disorder whose neurobiological basis is incompletely understood. Whole-brain trichotillomania neuroimaging studies are lacking.

Aims
To investigate grey and white matter abnormalities over the whole brain in patients with trichotillomania.

Method
Eighteen patients with DSM–IV trichotillomania and 19 healthy controls undertook structural magnetic resonance imaging after providing written informed consent. Differences in grey and white matter were investigated using computational morphometry.

Results
Patients with trichotillomania showed increased grey matter densities in the left striatum, left amygdalo-hippocampal formation, and multiple (including cingulate, supplementary motor, and frontal) cortical regions bilaterally.

Conclusions
Trichotillomania was associated with structural grey matter changes in neural circuitry implicated in habit learning, cognition and affect regulation. These findings inform animal models of the disorder and highlight key regions of interest for future translational research.

Declaration of interest
None. Funding detailed in Acknowledgements.

Trichotillomania is an impulse control disorder characterised by repetitive hair-pulling that leads to noticeable hair loss and functional impairment (DSM–IV).1 Unfortunately, the majority of sufferers have never been diagnosed and have never received treatment.2 Peak age at onset is 12–13 years, and hair-pulling most commonly affects the scalp and eyelashes/eyebrows.2 There have been no population-wide epidemiological studies of the condition. Based on a survey conducted in 2500 college students, lifetime prevalence has been estimated to be 0.6–2.5%.3 There have been no population-wide epidemiological studies of the condition. Based on a survey conducted in 2500 college students, lifetime prevalence has been estimated to be 0.6–2.5%.3 Trichotillomania has phenomenological overlap with obsessive–compulsive disorder and Tourette syndrome, and consequently represents a candidate member of the obsessive–compulsive spectrum.4 Neurobiological models of these other conditions posit dysregulation of neural circuitry involved in habit formation and top-down inhibitory control, based on tiers of evidence from neuroimaging and elsewhere.5,6 There have been no brain-wide structural studies of trichotillomania, which hampers our understanding of its neurobiological profile and overlap with other obsessive–compulsive disorders.7

In comparison with other related conditions where compulsivity is also a prominent component, trichotillomania offers advantages in terms of neuroscientific investigation. Studies of obsessive–compulsive disorder and Tourette syndrome have often been confounded by current medications. The lack of established treatment guidelines for trichotillomania, and lack of public/clinician awareness, facilitates recruitment of patients who are not medicated to avoid this confound. It is difficult to model intrusive obsessional thoughts or complex vocal tics in animals. By contrast, hair-pulling is a relatively specific behaviour that occurs across species and several promising animal models exist. Mice with disruption of the HoxB8 gene, which is involved in neuronal development, exhibit pathological grooming behaviour.7 The HoxB8 gene is expressed in multiple brain regions, including the striatum and cingulate cortex. Mice with genetic deletion of a postsynaptic scaffolding protein expressed in the striatum (SAP90/PSD95-associated protein) exhibit compulsive grooming behaviour leading to hair-loss and skin lesions.8

Although these translational models implicate developmental abnormalities of the striatum and cortex in pathological hair-pulling, and neurobiological overlap between trichotillomania and obsessive–compulsive disorder has been suggested, there have been no whole-brain studies of the disorder with which to validate these approaches. Extant trichotillomania neuroimaging studies have all used region-of-interest approaches, rather than exploring distributed abnormalities over the whole brain. Therefore, critically implicated regions may have been overlooked. This is particularly relevant when considering obsessive–compulsive-spectrum disorders, which are theoretically underpinned by abnormalities in large-scale brain systems, i.e. neurocognitive circuits, rather than lesions within a discrete region.9,10

O’Sullivan et al11 reported reduced left putamen volumes in a sample of 10 patients with trichotillomania v. 10 healthy controls. However, these results were described by the authors as preliminary owing to the relatively small sample size and lack of correction for multiple comparisons. Stein et al found no evidence for caudate volume abnormalities in 7 patients with trichotillomania compared with 12 controls using magnetic resonance imaging (MRI) (putamen volumes were not assessed).12 Keuthen et al reported reduced cerebellar volumes in a sample of 14 patients with trichotillomania v. 12 controls, using MRI parcellation techniques.13 Grachev investigated MRI abnormalities in 10 patients with trichotillomania v. 10 controls.14 No significant abnormalities were detected in the initial analysis, although a broader analysis of 48 parcellated regions (without correction for multiple comparisons) identified reduced left inferior frontal gyrus volumes and increased right cuneal cortex volumes. Thus, there exists inconsistent evidence for structural abnormalities of the striatum, frontal regions and cerebellum in trichotillomania.

The aim of the present study was to objectively investigate grey and white matter abnormalities over the whole brain in...
unmedicated patients with trichotillomania. We accomplished this by using cluster-based permutation analysis, which enabled automated, sensitive and unbiased analysis with correction for multiple comparisons. In light of the above discussion, it was predicted that trichotillomania would be associated with structural abnormalities of large-scale brain networks, including the striatum and cortex.

Method

Participants

Patients with trichotillomania were recruited via support websites, and controls were recruited via newspaper advertisements in the UK. Prior to enrolment, all participants undertook an extended clinical interview conducted by a member of the study team using the Mini International Neuropsychiatric Inventory (MINI), a well-validated screening instrument for DSM–IV Axis I disorders. Twenty people with trichotillomania and 19 healthy volunteers were enrolled after providing written informed consent and meeting eligibility criteria. For trichotillomania, inclusion criteria were fulfilment of DSM–IV diagnostic criteria (as ratified by a consultant psychiatrist), no treatment for >6 months, and no prior history of neurological conditions such as tic-spectrum disorders and epilepsy. Further, we excluded patients with current depression (defined as meeting MINI criteria and/or having a Montgomery–Åsberg Depression Scale (MADRS) total score >10) and current obsessive–compulsive disorder (defined as meeting MINI criteria and/or having a Yale–Brown Obsessive Compulsive Scale total score >10). We measured IQ using the National Adult Reading Test (NART). Trichotillomania disease severity was assessed using the Massachusetts General Hospital (MGH) Hair pulling Scale. Controls were included on the basis of no history of neurological or Axis I disorders. All volunteers were deemed safe for MRI by completion of a screening questionnaire and the study was approved by a local research ethics committee.

Neuroimaging

Structural MRI scans were acquired from all participants using a 1.5 T GE Signa system (General Electric, Milwaukee, USA) at the Department of Radiology, Addenbrooke’s Hospital, Cambridge, UK. Axial three-dimensional (3-D) T1-weighted images were obtained using a spoiled gradient recall sequence with the parameters: 124 slices of thickness 2 mm, repetition time (TR) = 33 ms, echo time (TE) = 3 ms, flip angle 40°, matrix size 256 × 256 and in-plane voxel dimensions 0.94 mm².

Results

Routine clinical screening of MRI scans identified significant structural abnormalities in two patients, whose data were excluded from the subsequent analysis. One patient’s scans showed a basal ganglia signal hyperintensity; this was deemed of uncertain clinical significance and the patient was asked to monitor for worsening of symptoms or onset of new symptoms. The other patient’s scans showed evidence of a brainstem event, leading to urgent clinical follow-up. Thus, the final sample size was 18 patients and 19 controls. As can be seen in Table 1, the two study groups did not differ significantly in terms of age, NART IQ, male:female ratio, and handedness. Total MADRS scores for both groups were well below the threshold for clinically significant depression; as anticipated, patients showed significantly higher scores than healthy controls. The mean total MGH score at the time of study participation for the patients was 15.11 (s.d.=4.54), consistent with mild to moderate disease severity. One patient met DSM criteria for persistent panic disorder and agoraphobia; the others were free from current Axis I comorbidities according to MINI screen. The mean age of symptom onset reported by patients was 11.89 years (s.d.=6.85).

The patients did not differ significantly from controls in terms of global grey matter density (trichotillomania 9.26 arbitrary units (s.d.=0.47), controls 9.14 (s.d.=0.66), P=0.51). In comparison with the healthy volunteers, patients with trichotillomania showed grey matter density excesses in three clusters (see Fig. 1 and Table 2 for anatomical details and peak MNI coordinates). These comprised: (a) a mean density increase of 18% in the striatum (left putamen) and limbic system (left amygdalo-hippocampal complex); (b) a mean density increase of 23% in bilateral fronto-temporal lobes (cingulate, supplementary motor and superior cortices);
and (c) a mean density increase of 21% in left occipital and parietal regions (Fig. 2). These results were not dependent on entering age as a covariate, since when the analysis was rerun without age as a covariate, the core results were still evident (i.e. increased grey matter in the left amygdalo-hippocampal formation, bilateral cingulate, and right middle/superior frontal cortices). There were no significant regions of relative grey matter reductions or changes in white matter (increases or decreases) in the patients. No clusters were found in which density covaried significantly with symptom severity in the patients. No significant correlations were found between mean grey matter densities and patient disease severity scores, in those clusters identified in the between-group analysis ($P>0.10$).

**Discussion**

The key finding of this study was that unmedicated patients with trichotillomania exhibited abnormally increased grey matter densities compared with matched healthy controls in the left amygdalo-hippocampal complex, left striatum and multiple
patients with trichotillomania showed deficits on tests of divided attention, which likely impede quality of life. In neuropsychological studies, structural abnormalities detected in these regions in trichotillomania suggest involvement of the basal ganglia in the development of pathological habits.5,40 Striatal involvement in trichotillomania is reminiscent of obsessive–compulsive disorder, has been shown to disrupt the ability to perform choreographed grooming and habit learning, there being some evidence that striatal damage in rats can reflect deviation from normal developmental trajectories. Alternatively, they may reflect neuroplastic changes occurring through use of brain regions involved in grooming and habit learning, there being some evidence that increases in grey matter can occur through motor-skill training.39

The striatum is thought to play a critical role in habit learning and in the chunking of automated action sequences, according to tiers of evidence from animals and humans.5,41 Striatal damage in rats has been shown to disrupt the ability to perform choreographed grooming sequences.44 In humans, clinical data suggest that the striatum is responsible for the gradual incremental learning of associations typical of habit learning,39 Striatal involvement in trichotillomania is reminiscent of obsessive–compulsive disorder, and supports a similar conceptualisation emphasising the role of the basal ganglia in the development of pathological habits.39,40 Cortical regions such as the cingulate and prefrontal lobes are involved in multiple high-level cognitive processes.41 The structural abnormalities detected in these regions in trichotillomania could mediate cognitive problems previously identified in patients, which likely impede quality of life. In neuropsychological studies, patients with trichotillomania showed deficits on tests of divided attention,42 response inhibition and working memory.43,44 The relationship between grey matter excesses and cognitive deficits in patients with trichotillomania merits follow-up, since these neural regions and their dependent cognitive functions represent targets for novel cognitive enhancers.45

The finding of amygdalo-hippocampal abnormalities was not predicted a priori. The amygdalo-hippocampal formation constitutes part of the limbic system, which regulates arousal and emotional learning processes.46 Several studies support a causal relationship between increased or decreased arousal and hair-pulling episodes, and between negative affect and hair-pulling episodes.47–49 Furthermore, trichotillomania has been associated with childhood trauma and post-traumatic stress disorder. In one survey, the majority of patients reported physical abuse and/or emotional neglect as a trigger in childhood.50

Positive features of this study include the use of permutation cluster analysis to maximise power while facilitating corrected whole-brain analysis, and the inclusion of patients who were untreated for at least 6 months prior to scanning. None the less, several caveats must be considered. Details of past treatments (beyond 6 months) received by patients were not available, to explore whether past treatment-seekers differed from non-treatment-seekers. It remains to be seen whether the present findings generalise to other groups of patients with trichotillomania who differ in terms of their clinical characteristics (past treatments, disease severity, comorbidities). Another potential limitation is that patients showed significantly higher MADRS (dysphoric mood) scores than controls, despite being free from DSM–IV depression. However, we controlled for this by entering MADRS scores as a covariate into the imaging analysis. Finally, voxel-based morphometry techniques carry potential limitations such as confounds due to choice of smoothing kernel size and potential misalignment of brain structures during normalisation. On the other hand, such techniques enable objective and sensitive analysis, with stringent correction for false positives over the whole brain.51

This study, using a cluster-level technique to investigate trichotillomania, provides an objective whole-brain-based analysis that directs researchers to areas that are abnormal in this disorder, namely cortical regions, the amygdalo-hippocampal formation and the striatum. These results suggest overlap with other putative obsessive–compulsive-spectrum disorders in terms of neurobiology.6,40 The functional significance of these grey matter abnormalities requires clarification in follow-up longitudinal studies, and in studies of unaffected first-degree relatives (asymptomatic individuals at increased genetic risk). The further application of translational neuroscientific techniques to the study of trichotillomania will extend these findings and provide new insights into its neurobiology, with implications for diagnosis and treatment of trichotillomania and related obsessive–compulsive-spectrum disorders.

**Fig. 2** Grey matter densities in healthy controls and patients with trichotillomania for each of the three clusters identified in the permutation analysis.

Cluster 1, left hippocampus, left amygdala, left putamen; Cluster 2, bilateral anterior/middle cingulate, bilateral supplemental motor area, bilateral fronto-superior cortices; Cluster 3, left superior/middle occipital cortex, left superior/inferior parietal cortex.

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The Most Serious Moment of Our Lives

Ron Charach

Years later as Mindy began to unravel, and rolled on the hospital floor when she failed to get her way, her second drink of lye impressing not one soul in her exhausted family, they all agreed to plug her into the wall when the fourth and final round of pills failed to work. Wheel her back when you’re finished, head turned over on its side so she can’t breathe her vomit, meaning no aspiration.

But when her eyes unsealed in the white tiled room, and she hoarsely called for water, she recognized my role in this, my professional ring through the plastic. She may have seen a liar straining to escape from my face, because instead of asking about her husband and the kids, and who knew, and did everybody know, instead, she turned her electric breath on me. Automatically, I told her, “Shhh, it’s okay now . . .” but she looked me up and down and said, “This is the most serious moment of our lives.”

Ron Charach was born in Winnipeg, Canada. He studied medicine in Toronto and trained in psychiatry in New York. He has lived in Toronto since 1980. The two poems are from Selected Portraits. Hamilton, Wolsak & Wynn Publishers.

Poem selected by Femi Oyebode.