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Duration of Illness and Cortical Thickness in Trichotillomania: Preliminary Evidence for Illness Change Over Time

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Abstract

Trichotillomania is a psychiatric condition characterized by repetitive pulling out of one's hair, leading to marked functional impairment. The aim of this study was to examine the association between duration of trichotillomania (defined as time between initial age of onset and current age) and structural brain abnormalities by pooling all available global data. Authors of published neuroimaging studies of trichotillomania were contacted and invited to contribute de-identified MRI scans for a pooled analysis. Freesurfer pipelines were used to examine whether cortical

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Declaration of Interest

Dr. Grant has received research grants from TLC Foundation, and Takeda Pharmaceuticals. Dr. Grant receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies and has received royalties from Oxford University Press, American Psychiatric Publishing, Inc., Norton Press, and McGraw Hill. Dr. Chamberlain's time on this study was supported by a Wellcome Trust Clinical Fellowship (110049/Z/15/Z). Dr. Chamberlain consults for Cambridge Cognition, Shire, Promentis, and Ieso Digital Health. Dr. Chamberlain receives a stipend for his work as Associate Editor at Neuroscience and Biobehavioral Reviews; and at Comprehensive Psychiatry. Dr. Keuthen is on the Scientific Advisory Board of the TLC Foundation for BFRBs and currently receives funding from its BFRB Precision Medicine Initiative. She receives royalties from New Harbinger, Inc. In the past 3 years, Dr. Stein has received research grants and/or consultancy honoraria from Biocodex, Lundbeck, Servier, and Sun. Dr. Lochner reports no potential conflicts of interest.

Author Contribution

All authors contributed to the design of the study, carrying it the study, analyzing the data and writing the article.

thickness and sub-cortical volumes were associated with duration of illness in adults with trichotillomania. The sample comprised 50 adults with trichotillomania (100% not taking psychotropic medication; mean [SD] age 34.3 [12.3] years; 92% female). Longer duration of illness was associated with lower cortical thickness in bilateral superior frontal cortex and left rostral middle frontal cortex. Volumes of the a priori sub-cortical structures of interest were not significantly correlated with duration of illness (all $p > 0.05$ uncorrected). This study is the first to suggest that trichotillomania is associated with biological changes over time. If this finding is supported by prospective studies, it could have important implications for treatment (i.e. treatment might need to be tailored for stage of illness). Viewed alongside prior work, the data suggest that brain changes in trichotillomania may be differentially associated with vulnerability (excess thickness in right inferior frontal cortex) and with chronicity (reduced thickness in medial and superior frontal cortex). Longitudinal research is now indicated.

Keywords

trichotillomania; duration of illness; MRI; neuroimaging; cortical thickness

Introduction

Trichotillomania is a psychiatric condition characterized by recurrent pulling out of one's own hair, leading to hair loss (APA, 2013). Brain imaging studies have suggested that the pathophysiology of trichotillomania is linked to abnormalities in both cortical regions (associated with top-down control and habit suppression) and sub-cortical neural regions (such as the dorsal striatum involved in habit generation) (Chamberlain et al., 2009, Chamberlain et al., 2010; Chamberlain et al., 2018; Grant et al., 2018; Isobe et al., 2018; Olduag et al., 2014; Slikboer et al., 2018; White et al., 2013). The findings from imaging studies in trichotillomania, however, have not always shown consistent findings (see Roos et al., 2013 no differences in trichotillomania compared to controls in white matter tracts of the fronto-striatal-thalamic pathway), and this raises the question as to whether trichotillomania is a heterogeneous disorder. Previous neuroimaging studies have examined brain abnormalities in individuals with current trichotillomania but have not examined the impact of symptom chronicity (duration of illness or clinical stage) on brain structure in patients – an issue that could be important in better understanding the heterogeneity of a disorder. Studies with other disorders have shown the importance of duration of illness/clinical staging in their presentation. In the case of substance use disorders, studies have suggested that longer duration of illness is correlated with more cognitive deficits (e.g., response inhibition and cognitive flexibility Laloyaux et al., 2012; Monterosso et al., 2005). Studies have further found that longer duration of illness may be associated with structural abnormalities such as gray and white matter volumes reductions, as well as decreased brain activation, in substance use disorders (Bjork et al., 2003; Ersche et al., 2011; Sjoerds et al., 2014, bipolar disorder (in the area of the hippocampus and amygdala; Gildengers et al., 2014), body dysmorphic disorder (right orbitofrontal cortex volumes; Buchanan et al., 2014), and obsessive-compulsive disorder (hippocampus and amygdala; Atmaca et al., 2008).

Although clinical stage seems to be an important issue in understanding psychiatric disorders, no study has specifically investigated how this variable might affect our understanding of neuroimaging results in trichotillomania. Therefore, our objective in this study was to investigate structural neuroimaging results associated with different durations of illness in a large pooled sample of adults with trichotillomania. Toward that end, the current study obtained available MRI scans (along with select demographic and clinical information) from research groups that have published peer-reviewed data papers of trichotillomania and examined cortical thickness and sub-cortical structure volumes. We hypothesized that longer duration of illness in trichotillomania would be associated with cortical thickness abnormalities in frontal cortical sectors coupled with excess volume of the dorsal striatum (putamen/caudate).

Methods

Participants

All structural MRI studies regarding trichotillomania were identified via PubMed in May 2019. We contacted the authors of these publications and invited them to contribute de-identified MRI scans from published studies. Written informed consent was obtained from all participants, and the original studies each received Institutional Review Board approvals. Conventional cortical data for many in the current sample were reported previously and the MRI dataset obtained here was largely overlapping versus that used by a previous pooled study (Chamberlain et al., 2018); the previous paper did not examine the duration of illness measure nor how it related to brain structure. Readers are referred to the original paper (and its supplement) for available information about diagnostic criteria used at each site, the scanner type, etc. The reason overlap was not exact is that duration of illness was not available for all patients in the original dataset – patients were not always able to describe their duration of illness; or the information was not recorded for other reasons (e.g. missing, or participant declined to provide). In the current paper, data were included only from subjects who provided duration of illness information. The numbers of patients whose data was included from different research groups were as follows: 25 from Professor Lochner's unit (Stellenbosch University), 7 from Professor Keuthen's unit (Massachusetts General Hospital and Harvard Medical School), 13 from Dr Chamberlain's unit (University of Cambridge), and 5 from Professor Grant's Unit (University of Chicago).

Assessments

Demographic data consisted of age, gender, level of education, psychotropic medication status, and severity of illness as measured with the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) (Keuthen et al., 1995), a self-report questionnaire assessing severity of trichotillomania. Duration of illness was determined using self-report and calculated from the initial onset of any pulling behavior to their current age.

Imaging pre-processing and data extractions were undertaken on the University of Chicago Midway computing system. MRI scans were processed using FreeSurfer software (surfer.nmr.mgh.harvard.edu) a methodology that has previously been validated (Dale et al., 1999; Reuter et al., 2012). In brief, scans for each subject were standardized, bias-field

corrected, and skull-stripped. Cortical surfaces were identified using automated algorithms, normalized to the standard Freesurfer template, and smoothed using a standard 10 mm full width half maximum (FWHM) kernel. The Desikan-Killiany Atlas was used. Volumes of *a priori* sub-cortical structures of interest were also extracted using the Freesurfer pipeline (caudate, putamen, and nucleus accumbens).

Data Analysis

Relationships between duration of illness and brain structure were explored using (i) the Freesurfer QDec tool for cortical regions (voxel-wise threshold of $p < 0.001$, Cluster-wise Corrected for Multiple comparisons at $p < 0.05$ using Monte Carlo Permutation) (Hagler et al., 2006); and (ii) Spearman's r correlation tests for the *a priori* subcortical regions ($p < 0.05$ Bonferroni corrected for the number of sub-cortical regions examined, i.e. p threshold $0.05/6 = 0.0083$, since there were three structures per hemisphere). Age was controlled for in all the statistical analyses. Post hoc, potential confounding effects of the following variables on the results were explored: gender, education level, and symptom severity. This was done by exploring whether: cortical thickness in the brain regions associated with duration of illness were correlated with symptom severity (MGH total scores, spearman's r tests); and by comparing cortical thickness in these regions as a function of gender and education level (Wilcoxon tests).

using appropriate tests to assess relationships with cortical thickness in any identified brain regions related to duration of illness (spearman's r , or between-group comparisons using analysis of variance, as appropriate): severity (MGH total scores), presence of comorbidities, education levels.

Results

The study sample comprised 50 adults with trichotillomania (92% female; mean [SD] age=34.2 [12.3] years) who also had data regarding the duration of their illness. The mean total MGH-HPS severity score was 15.1 [4.4], consistent with, on average, mild-moderate illness; and the mean duration of illness was 21.5 [13.0] years. Of 44 people for whom education level data were available, 29 (58%) had graduate/higher degree level education, six (12%) had college/lower degree level education, and eight (16%) had less than college level education (i.e. did not attend or did not complete college). All participants were free from current psychotropic medications.

Freesurfer analysis yielded three significant clusters in which duration of illness was associated with cortical thickness. As shown in Figure 1, longer duration of illness was associated with lower cortical thickness in bilateral superior frontal cortex, and left rostral middle frontal cortex. Volumes of the *a priori* sub-cortical structures of interest were not significantly correlated with duration of illness (all $p > 0.05$ uncorrected, data not shown). Correlation plots between duration of illness and cortical thickness in each significant cluster are shown in the Supplement.

Cortical thicknesses in the brain regions related to duration of illness were not significantly correlated with disease severity (MGH total scores) (all $p > 0.20$); nor did they differ as a function of gender (all $p > 0.20$), nor education levels (all $p > 0.10$).

Discussion

This study supports the hypothesis that longer duration of illness is associated with reduced cortical thickness in the left rostral middle frontal cortex and bilaterally in the superior frontal cortices, in trichotillomania. As such, this study is the first to show that the illness of trichotillomania is associated with potentially progressive biological changes over time. If this finding is supported by prospective studies, it could have important implications for treatment (i.e. would someone with five years of trichotillomania be treated differently from someone with twenty years of trichotillomania? Or would there be other markers to look for over time that would guide treatment?).

The finding that reduced cortical thickness in particular frontal regions is associated with chronicity in trichotillomania merits consideration in light of previous case-control studies of the disorder. One study examined cortical thickness in trichotillomania and found excess thickness in patients versus controls in the right inferior/middle frontal cortex, right lingual gyrus, left temporal cortex, and left precuneus (Odlaug et al., 2014). In another study of pooled participants from several sites, trichotillomania subjects compared to controls showed significantly increased cortical thickness in a cluster at the right inferior frontal gyrus (Chamberlain et al., 2018). These studies were both comparisons of trichotillomania to controls, whereas the current study was examining changes in trichotillomania over time (i.e. duration of illness). Viewed collectively, the data suggest that excess cortical thickness is observable in trichotillomania compared to controls in certain cortical regions (notably right inferior frontal gyrus); whereas potentially progressive reductions in cortical thickness in other frontal regions (more rostral/middle and superior frontal regions) occur in patients. As such, prospective studies are now indicated to better understand differential brain-based markers associated with vulnerability versus chronicity.

What explains the association between longer duration of illness and reduced cortical thickness? One theory is that cortical thinning may be due to the progressive effects of trichotillomania, that is, cortical thinning occurs due to repetitive engagement in unhealthy mental activities such as hair pulling. Despite the social and self-esteem problems that often arise from the alopecia, individuals with trichotillomania report being unable to control their behavior (Diefenbach et al., 2005), and on a cognitive level, this has been supported by deficits in aspects of inhibition (Bohne et al., 2008; Brennan et al., 2016; Chamberlain et al., 2009). These clinical and cognitive characteristics are consistent with abnormalities of the frontal cortex. If these deficits are due to the cortical thickness of frontal regions, however, it is unclear why the longer duration of illness and its concomitant reduced thickness are not also associated with worsening clinical symptoms, though this could be accounted for if the right inferior frontal changes constitute a vulnerability rather than chronicity marker, there being evidence that this region bears a particularly strong relationship with inhibitory control (Aron et al., 2004). In terms of the clinical symptoms we have captured, no such link exists between worse hair pulling symptoms and longer duration of illness, but perhaps our scales

fail to detect more subtle worsening of symptomatology. Future research should examine whether the findings from this study have the ability to predict treatment response.

This study has several positive features including it being the first study examining duration of illness and its associations with cortical thickness in trichotillomania. Several limitations, however, should be considered. Duration of illness was quantified using self-report (difference between age at onset and age at study participation). Recall of such information can be affected by bias; more accurate information was not available (such as from historical medical notes) due to the nature of the study. The sample size may have limited statistical power to detect more subtle cortical thickness changes associated with duration of illness. These results also come from a relatively small and homogeneous sample; patients were of average mild-to-moderate disease severity. The sample also was comprised of people who had and had not received treatment (sometimes multiple interventions, while others had never received treatment), as well as those with comorbidities, and these treatment histories and comorbidities may have produced subtle changes that confound a clear association between duration of illness and cortical thickness. Because historical information on previous diagnoses was not available to us, we could not control for this issue. It is also possible that self-report age of onset may not always be reliable. Nonetheless, no patients were receiving psychotropic medication at the time of study participation, so shorter-term effects of psychotropic medication on brain structure can be ruled out. There are potential problems when pooling imaging data from different sites; due to the retrospective nature of the study, and small sample sizes, we could not compare findings across sites or ensure the same imaging technology and scan parameters were used. Longitudinal imaging studies, in large sample sizes (ideally using standardized imaging protocols) would be beneficial to the field and allow for a better establishment of the causal relationship between the neural findings and duration of illness.

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Figure 1. Regions significantly associated with duration of illness in trichotillomania, at Cluster-Corrected $p < 0.05$.

In all cases, longer duration of illness was associated with lower cortical thickness. **Top panel, left hemisphere**, Cluster 1 (light blue, cluster-wise $p = 0.00010$) was maximal in the rostral middle frontal cortex (size 1770 mm^2 ; Talairach co-ordinates $[X, Y, Z] = [-39.0, 28.8, 28.7]$); and Cluster 2 (dark blue, cluster-wise $p = 0.00820$) was maximal in the superior frontal cortex (size 1185 mm^2 ; $[-13.2, 52.5, 21.3]$). **Bottom panel, right hemisphere:** Cluster 3 (dark blue, cluster-wise $p = 0.00910$) was maximal in the superior frontal cortex size 1183 mm^2 , $[12.0, 12.5, 38.9]$.