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Impaired response inhibition and excess cortical thickness as candidate endophenotypes for trichotillomania

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ABSTRACT

Trichotillomania is characterized by repetitive pulling out of one's own hair. Impaired response inhibition has been identified in patients with trichotillomania, along with gray matter density changes in distributed neural regions including frontal cortex. The objective of this study was to evaluate impaired response inhibition and abnormal cortical morphology as candidate endophenotypes for the disorder. Subjects with trichotillomania ($N = 12$), unaffected first-degree relatives of these patients ($N = 10$), and healthy controls ($N = 14$), completed the Stop Signal Task (SST), a measure of response inhibition, and structural magnetic resonance imaging scans. Group differences in SST performance and cortical thickness were explored using permutation testing. Groups differed significantly in response inhibition, with patients demonstrating impaired performance versus controls, and relatives occupying an intermediate position. Permutation cluster analysis revealed significant excesses of cortical thickness in patients and their relatives compared to controls, in right inferior/middle frontal gyri (Brodmann Area, BA 47 & 11), right lingual gyrus (BA 18), left superior temporal cortex (BA 21), and left precuneus (BA 7). No significant differences emerged between groups for striatum or cerebellar volumes. Impaired response inhibition and an excess of cortical thickness in neural regions germane to inhibitory control, and action monitoring, represent vulnerability markers for trichotillomania. Future work should explore genetic and environmental associations with these biological markers.

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1. Introduction

Trichotillomania (also known as Hair Pulling Disorder) is an often debilitating psychiatric condition characterized by recurrent pulling out of one's own hair, leading to hair loss and marked functional impairment (Odlaug et al., 2010; Woods et al., 2006). While the phenomenon of hair pulling has been described since antiquity (such as in work attributed to Hippocrates), trichotillomania was first recognized as a distinct clinical entity by the French dermatologist Francois Hallopeau in the 19th Century (Hallopeau, 1889). Subsequently, trichotillomania was incorporated into psychiatric nosology, first as an Impulse Control Disorder in the Diagnostic and Statistical Manual 3rd Edition (DSM-III-R), and then as an Obsessive Compulsive Related Disorder in the 5th Edition (DSM-5). The clinical and research importance of trichotillomania is increasingly recognized. Far from being rare, trichotillomania is relatively common, with point prevalence estimates of 0.5–4% (Odlaug and Grant, 2010) and lifetime prevalence estimates of around 0.6% (Christenson et al., 1991). Animal models of excessive grooming have been widely touted as being valuable not only in understanding the neurobiology human trichotillomania, but also other disorders more broadly, especially obsessive compulsive disorder (OCD) (e.g. Greer and Capecchi, 2002; Zuchner et al., 2006; Chen et al., 2010, for review see Camilla d'Angelo et al., 2014). Despite this surge of interest, the neurobiological basis of trichotillomania in humans has received scant research attention to date.

Trichotillomania is a highly familial illness (Keuthen et al., 2014). Genetic and environmental factors and their interactions are likely important in its pathogenesis (Keuthen et al., 2014; Novak et al., 2009; Chattopadhyay, 2012), but the precise nature of these factors and their relation with cognitive function and brain structure

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have not yet been identified. There is a search in psychiatry for objective intermediate biological markers, ideally grounded in the neurosciences, which signal 'risk' of developing a given disorder (termed 'endophenotypes') (Gottesman and Gould, 2003). Endophenotypes by definition exist not only in patients with a given disorder but also in their clinically unaffected first-degree relatives, as compared to individuals with no known family history of the condition. While considerable progress has been made in identifying candidate endophenotypes for OCD (Fineberg et al., 2010), no studies have examined biological markers in unaffected relatives of people with trichotillomania.

The brain basis of trichotillomania is unclear; likely there are several key facets of the illness. One model emphasizes three key features: Affect dysregulation, behavioral 'addiction' and cognitive dyscontrol (Stein et al., 2006). Emotion dysregulation can play a role in the maintenance of trichotillomania, in that hair pulling may act to modulate high arousal and low arousal states (Penzel, 2003; Stein et al., 2006; Diefenbach et al., 2008). Hair pulling can also be considered as a candidate behavioral addiction in view of certain parallels with substance addiction (Grant et al., 2007). For example, craving to pull hair can escalate over time and this can be transiently relieved by undertaking the act; treatments of utility in substance dependence show promise for trichotillomania, e.g. opiate antagonists and glutamate modulators (Grant et al., 2009, 2014). Cognitive dyscontrol is suggested by neuropsychological assessments conducted in patients with trichotillomania. Trichotillomania is associated with impaired inhibitory control (Chamberlain et al., 2006; Odlaug et al., 2012), as measured by the Stop-Signal Task (SST), a widely used translational computerized paradigm dependent on the integrity of the right inferior gyrus and other circuitry (Aron et al., 2014).

Neuroimaging represents a central means of exploring the contribution of neural regions relevant to emotional processing, behavioral addiction, and cognitive control, to the manifestation of trichotillomania. Earlier studies found evidence for structural abnormalities in relevant neural regions, such as reduced gray matter in the putamen and left inferior frontal gyrus and increased gray matter in the right cuneus (Grachev, 1997; O'Sullivan et al., 1997); and reduced cerebellar volumes (Keuthen et al., 2007). The majority of studies to date utilized a region-of-interest (ROI) approach for examining cortical abnormalities: this approach relies on pre-existing knowledge of neurobiology (which is limited for trichotillomania) and can lead to abnormalities in other regions being overlooked (for discussion and review see Chamberlain et al., 2009). Using a whole brain voxel-based morphology (VBM) (rather than ROI) approach, excess gray matter density has been found in patients with trichotillomania compared to controls, in the striatum, amygdalo-hippocampal formation, frontal and cingulate cortices, and supplementary motor cortex (Chamberlain et al., 2008, 2009). In a recent functional neuroimaging study, patients with trichotillomania exhibited dampening of nucleus accumben responses to reward anticipation (but relative hypersensitivity to gain and loss outcomes) as compared to controls (White et al., 2013). Another fMRI study did not identify abnormal neural activation during implicit sequence learning in patients versus controls (Rauch et al., 2007).

In terms of brain structure analysis techniques, the VBM approach is not without its critics: it potentially confounds several parameters, including changes in gray matter thickness, intensity, cortical surface area, and cortical folding (Hutton et al., 2009; Voets et al., 2008; for discussion see Kuhn et al., 2013). Therefore, the alternative approach of surface-based morphology has been developed, which is capable of exquisite and sensitive characterization of cortical thickness (Dale et al., 1999; Kuperberg et al., 2003; Reuter et al., 2012).

To address these limitations, we undertook a study of response inhibition and brain structure in individuals affected by trichotillomania and their clinically asymptomatic first-degree relatives. We hypothesized that patients and relatives would show impaired inhibition, coupled with abnormal cortical morphometry in neural regions involved in inhibitory control (especially the right inferior frontal gyrus), along with reduced striatal and cerebellar volumes.

2. Materials and methods

2.1. Subjects

Subjects meeting full DSM-5 criteria for trichotillomania were recruited via media advertisements and a psychiatric clinic, on the basis of having at least one first-degree relative being willing to also participate in the research.

Inclusion criteria for trichotillomania subjects included: 1) Men and women aged 18–65 years with a current primary Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of trichotillomania; 2) no contraindication to MRI; and 3) having one or more first-degree relative willing to participate in the research, also aged 18–65 years, without trichotillomania or other current psychiatric disorder. Exclusion criteria included: 1) unstable medical illness; 2) current pregnancy or inadequate contraception; 3) thoughts of suicide; 4) history of bipolar disorder, dementia, or psychotic disorder; 5) past 12 months substance use disorder; 6) initiation of behavior therapy or psychotropic medications within the last 6 months; and 7) current use of illicit drugs based on urine toxicology.

For each subject, one clinically unaffected first-degree relative was also contacted and enrolled, on the basis of not having current trichotillomania or any other DSM-5 disorder (by preference, similarly aged same-gendered sibling were enrolled where possible). Healthy controls were recruited via media advertisements on the basis of no history of psychiatric disorders and no known history of trichotillomania or obsessive compulsive related disorders (for example, OCD, excoriation disorder, body dysmorphic disorder) in first-degree family members.

The study procedures were carried out in accordance with the ethical standards laid out in the latest version of the Declaration of Helsinki. The Institutional Review Board of the University of Chicago approved the study and the consent statement. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Procedures

All subjects first received a psychiatric, medical, and family history evaluation. Clinical instruments included the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998), the Massachusetts General Hospital Hairpulling Scale (MGH-HPS) (Keuthen et al., 1995), the Clinical Global Impressions Severity Scale (CGI-S) (Guy, 1976), and the Quality of Life Inventory (QoLI) (Frisch and Cornell, 1993).

To provide an objective index of inhibitory control, participants then undertook the computerized Stop-Signal Test (SST) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Logan et al., 1984; Aron et al., 2003); this was undertaken in a quiet testing environment outside of the scanner. The details of this task are described elsewhere (Logan et al., 1984; Aron et al., 2003). In brief, subjects viewed a series of directional arrows appearing on-screen one per time, and made rapid responses depending on the direction of each arrow (left button for left-facing arrow, and vice versa). On a subset of trials, an auditory stop-signal ('beep') occurred following presentation of the directional arrow, signaling

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