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White matter integrity in hair-pulling disorder (trichotillomania)

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ABSTRACT

Hair-pulling disorder (trichotillomania, HPD) is a disabling condition that is characterized by repetitive hair-pulling resulting in hair loss. Although there is evidence of structural grey matter abnormalities in HPD, there is a paucity of data on white matter integrity. The aim of this study was to explore white matter integrity using diffusion tensor imaging (DTI) in subjects with HPD and healthy controls. Sixteen adult female subjects with HPD and 13 healthy female controls underwent DTI. Hair-pulling symptom severity, anxiety and depressive symptoms were also assessed. Tract-based spatial statistics were used to analyze data on fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). There were no differences in DTI measures between HPD subjects and healthy controls. However, there were significant associations of increased MD in white matter tracts of the fronto-striatal-thalamic pathway with longer HPD duration and increased HPD severity. Our findings suggest that white matter integrity in fronto-striatal-thalamic pathways in HPD is related to symptom duration and severity. The molecular basis of measures of white matter integrity in HPD deserves further exploration.

1. Introduction

Hair-pulling disorder (trichotillomania, HPD) is a disabling condition that is characterized by repetitive hair-pulling resulting in hair loss. HPD may interfere with social relationships, family life and work, and has been associated with significant functional impairment (Woods et al., 2006). Currently defined as an impulsive control disorder not otherwise specified (DSM-IV), HPD has also been conceptualized as an obsessive–compulsive (OC) spectrum disorder due to partial overlaps with obsessive–compulsive disorder (OCD), Tourette's syndrome and stereotypic behaviors such as skin-picking (Lochner et al., 2005; Chamberlain et al., 2009; Ferrao et al., 2009).

A number of the putative OC spectrum disorders may be mediated by fronto-striatal circuitry (Boulougouris et al., 2009; Fineberg et al., 2010). Imaging data on HPD are somewhat inconsistent. A number of structural and imaging studies have found evidence of fronto-striatal abnormalities (Grachev, 1997; O'Sullivan et al., 1997; Keuthen et al., 2007). On the other hand, there is also data on alterations in a broad range of other areas (Chamberlain et al., 2009) implicating fronto-striatal-thalamic pathways. For example, in an investigation of structural abnormalities in HPD using computational morphometry (Chamberlain et al., 2008), there were increased grey matter densities in widespread areas including the prefrontal lobe, anterior cingulate, supplementary motor areas, striatum, amygdala and hippocampus.

To date, structural imaging studies in HPD have focused on structural grey matter abnormalities, rather than on white matter integrity. The introduction of diffusion tensor imaging (DTI) techniques allows specific assessment of white matter integrity. Chamberlain et al. (2010) undertook DTI in 18 subjects with HPD and found decreased fractional anisotropy (FA) in the anterior cingulate, orbitofrontal cortex, presupplementary motor areas and temporal lobe in HPD compared to healthy controls, indicating disruption in white matter integrity. These findings are partly consistent with DTI findings in OCD, where white matter abnormalities have been found in the fronto-striatal-thalamic pathways (Menzies et al., 2008).

In addition to FA, established DTI parameters include mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) (Alexander et al., 2007). MD represents a global average of all diffusion directions (Assaf and Pasternak, 2008), with increased MD suggesting damaged and/or disorganized white matter tracts. AD is a specific measure of diffusion along axons, which decreases when there is axonal damage (Harsan et al., 2006; Sun et al., 2006). RD measures perpendicular diffusion towards membranes, which is increased when myelin is damaged (Song et al., 2002, 2005). MD, AD, and RD have not yet been reported in HPD. We therefore undertook DTI of individuals with HPD and healthy controls to assess FA, MD, AD, and RD. The vast majority of individuals with

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HPD are female (Christenson et al., 1994; Chamberlain et al., 2007), and we therefore included only women. We hypothesized that there would be disruption of white matter integrity in the fronto-striatal-thalamic pathways in HPD, and that some of these disruptions would be associated with clinical variables such as HPD duration and HPD severity.

2. Methods

2.1. Subjects

Subjects with HPD were recruited based on referrals made by specialist psychiatrists, community based primary care practitioners, consumer advocacy organizations, and by means of media advertisements. Subjects were screened telephonically by a postgraduate research assistant whereafter prospective candidates were invited for an interview at the MRC Research Unit on Anxiety and Stress Disorders. Subjects provided written, informed consent to participate before they were screened. Screening was done by a clinical psychologist using the Mini International Neuropsychiatric Interview Plus (MINI Plus)—version 5 (Sheehan et al., 1998), and the Structured Clinical Interview for obsessive–compulsive spectrum disorders (SCID-OCSD) (Du Toit et al., 2001).

Subjects were included if they had no prior history of substance or alcohol abuse/dependence or psychotic disorders, and no current psychiatric comorbidity or significant physical or neurological illnesses. In addition, all subjects were female adults (>18 and <65 years of age), right-handed, and either free of psychotropic medications or on a stabilized treatment regime. HPD patients were included if they reported current hair-pulling, while healthy controls had no current psychiatric disorders.

The study was approved by the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences (Stellenbosch University) and conducted according to the ethical guidelines and principles of the international Declaration of Helsinki and the Medical Research Council Ethical Guidelines for Research.

2.2. Procedures

Screening and clinical assessments were completed in one session, followed by DTI imaging on another day. Subjects provided demographic and clinical information, including information on age of onset of HPD. HPD severity was assessed using the Massachusetts General Hospital Hair-pulling Scale (MGH-HPS; Keuthen et al., 1995). Current anxiety and depressive symptoms were assessed using the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959) and the Montgomery–Asberg Depression Rating Scale (MADRS; Davidson et al., 1986), respectively. Hand preference of subjects was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971) to include right-handed subjects. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

2.3. Diffusion tensor imaging

A 3 T Siemens Allegra Magnetom Scanner was used to acquire three diffusion weighted images, each volume having the following parameters: 30 diffusion directions with $b=1000$ s/mm^2; repetition time (TR)=8800 ms; echo time (TE)=88 ms; in-plane resolution of 2×2 mm^2; and slice thickness of 2.2 mm. A single unweighted volume ($b=0$ s/mm^2) was also acquired.

2.4. Image data and statistical analyses

Demographic and clinical data were analyzed using Statistica 10 (Statsoft Inc.). *T*-tests and the Mann–Whitney *U* test were applied depending on data distribution, to compare study groups in terms of age, anxiety and depressive symptoms, and IQ estimates.

DTI analyses were done in the FMRIB Software Library (FSL), using tract-based spatial statistics (TBSS) (Smith et al., 2006) and custom tools in MATLAB (Mathworks Inc, Natick, MA). TBSS is well suited for small cohort studies (Pierpaoli et al., 1996; Assaf and Pasternak, 2008) due to its robustness in limiting residual misalignment and partial voluming that are common limitations of voxel-based analysis in DTI (Friston and Ashburner, 2004). The technique considers voxels that are centrally located in white matter tracts common to the study cohort (Smith et al., 2006), so that statistical power is increased due to a smaller search volume and reduced multiple comparisons. TBSS is therefore recommended for full brain DTI analyses (Smith et al., 2006).

FSL was used to perform firstly eddy current correction on each of the three acquisitions separately, followed by pre-processing in MATLAB. The acquisitions were co-registered by applying affine transformations to all volumes using the unweighted volume ($b=0$ s/mm^2) of the first acquisition as a reference. Outliers were determined for every co-registered acquisition relative to the tensor estimate, by calculating the *Z*-value at the 25th and 75th percentiles and ignoring values three standard deviations away from the mean. Considering the removed outliers, the three acquisitions were averaged. Subsequently, FA images were created (in FSL) by fitting a tensor model to the raw diffusion data. Brain extraction was performed using the FSL BET utility (Smith, 2002). FA data were then aligned into common MNI space using the non-linear registration tool FNIRT (Andersson et al., 2007a, 2007b). The mean FA image was "thinned" to create a mean FA skeleton, representing the centre of the white matter tracts for each subject. Individually aligned FA data were mapped on the skeleton, whereafter the projection transformations were applied to MD, AD and RD data.

FSL randomise was used to investigate group differences in DTI parameters. Non-parametric unpaired *t*-tests, correlational analyses and linear regression analyses (5000 permutations per test) were used to compare HPD subjects with controls, and to investigate associations of FA, MD, AD and RD data with HPD duration, HPD severity, anxiety and depressive symptoms. Analyses were corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE) algorithm, considering $p<0.05$ as significant (Smith and Nichols, 2009). A cluster-based threshold of 3 was also applied to identify principal significant areas, at $p<0.05$. White matter areas were identified using the ICBM-81 white-matter atlas (Mori et al., 2005). Given the exploratory nature of this study, whole brain analyses were undertaken.

3. Results

Sixteen female ($n=16$) subjects with HPD and 13 control subjects were included in the study. Demographic and clinical data of subjects are summarized in Table 1. Subjects had IQ quotients within normal or average ranges. Two out of the 16 HPD patients were receiving SSRI treatment prescribed for HPD at the time of study participation: one subject was on sertraline (50 mg) and the other on fluoxetine (40 mg). Eleven patients had never received psychotropic drugs.

Table 1
Demographic and clinical data of subjects.

Variable	HPD subjects ($n=16$)	Controls ($n=13$)	Statistics
Age (years, S.D.)	33.5 (13.1)	30.7 (9.2)	$t=0.65$, $p=0.520$
IQ (mean, S.D.)			
Verbal IQ	113.5 (15.4)*	115.6 (13.0)	$t=-0.40$, $p=0.696$
Performance IQ	110.9 (10.8)*	118.5 (12.8)	$t=-1.70$, $p=0.101$
Total IQ	113.8 (13.5)*	119.2 (12.5)	$t=-1.08$, $p=0.289$
Age of HPD onset (years, S.D.)	14.4 (9.4)	–	–
HPD duration (mean years, S.D.)	19.1 (14.0)	–	–
MGH-HPS-total score (mean, S.D.)	14.5 (5.3)	–	–
HAM-A-total score (mean, S.D.)	6.1 (3.5)	3.6 (2.5)	$t=2.10$, $p=0.046$**
MADRS-total score (mean, S.D.)	6.4 (5.3)	2.4 (2.4)	$Z=2.21$, $p=0.027$**

S.D., standard deviation; *n*, sample size; IQ, intelligence quotient; MGH-HPS, Massachusetts General Hospital Hair-pulling Scale; HAM-A, Hamilton Anxiety Scale; MADRS, Montgomery–Asberg Depression Rating Scale.

* There were data for 15 HPD subjects.

** $p<0.05$.