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White matter connectivity reflects clinical and cognitive status in Huntington's disease☆,☆☆,★

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ABSTRACT

Objective: To investigate structural connectivity and the relationship between axonal microstructure and clinical, cognitive, and motor functions in premanifest (pre-HD) and symptomatic (symp-HD) Huntington's disease.
Method: Diffusion tensor imaging (DTI) data were acquired from 35 pre-HD, 36 symp-HD, and 35 controls. Structural connectivity was mapped between 40 brain regions of interest using tractography. Between-group differences in structural connectivity were identified using network based statistics. Radial diffusivity (RD) and fractional anisotropy (FA) were compared in the white matter tracts from aberrant networks. RD values in aberrant tracts were correlated with clinical severity, and cognitive and motor performance.
Results: A network connecting putamen with prefrontal and motor cortex demonstrated significantly reduced tractography streamlines in pre-HD. Symp-HD individuals showed reduced streamlines in a network connecting prefrontal, motor, and parietal cortices with both caudate and putamen. The symp-HD group, compared to controls and pre-HD, showed both increased RD and decreased FA in the fronto-parietal and caudate-paracentral tracts and increased RD in the putamen-prefrontal and putamen-motor tracts. The pre-HD_{close}, compared to controls, showed increased RD in the putamen-prefrontal and fronto-parietal tracts. In the pre-HD group, significant negative correlations were observed between SDMT and Stroop performance and RD in the bilateral putamen-prefrontal tract. In the symp-HD group, RD in the fronto-parietal tract was significantly positively correlated with UHDRS motor scores and significantly negatively correlated with performance on SDMT and Stroop tasks.
Conclusions: We have provided evidence of aberrant connectivity and microstructural integrity in white matter networks in HD. Microstructural changes in the cortico-striatal fibers were associated with cognitive and motor performance in pre-HD, suggesting that changes in axonal integrity provide an early marker for clinically relevant impairment in HD.

Introduction

Neuropathological processes in Huntington's disease (HD) primarily target medium spiny neurons of the striatum (Graveland et al., 1985). Neurodegeneration is also seen in pyramidal projection neurons in the motor and prefrontal cortices, and cingulate and angular gyri (Macdonald and Halliday, 2002; Thu et al., 2010). Together, these neurodegenerative changes are considered to be the cause of onset of

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clinical symptoms in HD (Thu et al., 2010). In contrast, the mechanisms underlying cognitive changes, which often appear several years before clinical diagnosis, remain largely unknown.

Disruption of structural connectivity in specific neural circuits has been proposed to be one of the possible mechanisms leading to early cognitive and motor changes in premanifest Huntington's disease (pre-HD) (Li and Conforti, 2013). Structural connectivity can deteriorate in HD due to axonal dysfunction and degeneration associated with huntingtin aggregates which can appear early in HD (reviewed by Li and Conforti, 2013). Hence, white matter atrophy is evident in T1-weighted neuroimaging studies of HD (Tabrizi et al., 2009; Thieben et al., 2002), with posterior-frontal white-matter degeneration apparent even in individuals far from onset (Tabrizi et al., 2009). Diffusion tensor imaging (DTI) studies of HD have also suggested selective microstructural changes in white matter encompassing cortico-striatal motor circuit, corpus callosum, periventricular region, corona radiata, and prefrontal cortex (Bohanna et al., 2011; Dumas et al., 2012; Rosas et al., 2006, 2010; Weaver et al., 2009).

DTI also enables investigation of axonal fibers between gray matter structures using tractography methods (Bohanna et al., 2011; Jones, 2008). DTI tractography has been used in HD to isolate structural connections in specific neuroanatomical circuits including the motor loop and fronto-striatal circuit (Bohanna et al., 2011; Dumas et al., 2012; Kloppel et al., 2008), providing evidence for circuit specific alterations in white matter microstructure in HD. For example, microstructural damage in the striatal nodes of the motor loop has been shown to be associated with motor dysfunction in HD (Bohanna et al., 2011). Structural connectivity changes of the fronto-caudal tracts have been shown not only to reflect years to onset, but also to be associated with oculomotor function in pre-HD (Kloppel et al., 2008). Moreover, reduced fiber connectivity between the prefrontal cortex and the caudate has been shown to reflect symptomatology in pre-HD (Kloppel et al., 2008). DTI-tractography has also been used to determine pairwise connections between gray matter structures in the brain enabling calculation of a structural connectivity matrix for individual subjects (Zalesky et al., 2010). Network-based statistical methods can be used to isolate network connections that are altered in disease from the connectivity matrix (Zalesky et al., 2010, 2011). The identification of structural networks in pre-HD and symp-HD may provide insight into early markers of disease progression in HD.

The aims of the current study were to identify cortico-striatal networks affected in pre-HD and symp-HD, determine the microstructural alterations in the axonal fibers connecting these pathways, and investigate the relationship between axonal microstructural changes and clinical, cognitive and motor functions in pre-HD and symp-HD. We hypothesized that structural connectivity in neural circuits connecting motor and prefrontal cortices with the caudate and putamen would be affected in both pre-HD and symp-HD. Microstructural white matter degeneration in symp-HD has been reported in the body of the corpus callosum, which structurally connects frontal and parietal areas (Rosas et al., 2010). We hypothesized that symp-HD individuals would show further white matter structural disconnectivity in the fronto-parietal network. Fronto-striatal neural circuits are crucial for cognitive control (Liston et al., 2006). We hypothesized that the microstructural integrity of the fronto-striatal tracts would be associated with cognitive dysfunction in both pre-HD and symp-HD. To test these hypotheses, tractography was used to identify the extent of axonal connectivity between 40 neocortico and striatal brain regions. A network-based statistical method (Zalesky et al., 2010) was used to isolate neuroanatomical networks that showed connectivity differences between the groups. DTI-based measures of radial diffusivity (RD) are thought to be sensitive to demyelinative processes (Song et al., 2005). We measured RD values from the tracts identified as aberrant in pre-HD and symp-HD, and investigated the relationship of RD changes with clinical severity, and cognitive and motor performance.

Methods

Participants

Thirty-five pre-HD, 36 symp-HD, and 35 healthy control volunteers were included in this investigation, all recruited as part of the Australian-based IMAGE-HD study (Georgiou-Karistianis et al., 2013, in press; Gray et al., 2013). Recruitment procedures and inclusion criteria have been published previously (Georgiou-Karistianis et al., 2013). Controls were matched to pre-HD participants for age, gender and IQ [National Adult Reading Test 2nd edition, NART-2 (Nelson et al., 1992)], an estimate of premorbid intelligence. One-way ANOVAs revealed no significant differences in age or IQ scores between the pre-HD group and controls, but significant differences in age between controls and symp-HD, and between pre-HD and symp-HD, respectively ($p < 0.05$). CAG repeat lengths in the expanded alleles of the participants ranged from 39 to 50 (42 ± 2 for pre-HD; 43 ± 2 for symp-HD). Similar to Tabrizi et al. (2009), inclusion in the pre-HD group was based on UHDRS total motor score ≤ 5. The average years to clinical onset for the pre-HD group was 15 ± 8 years, as determined by a formula based on age, and the number of CAG repeats (Langbehn et al., 2004). The average disease burden score (DBS; Penney et al., 1997) was 270 ± 53. Years since the diagnosis of symptom onset (ascertained by the clinician A.C.) in the symp-HD group ranged from 0 to 5 years with a mean DBS of 379 ± 70 for the group. Demographics, clinical information, and neurocognitive measures of interest are provided in Table 1. The complete battery of neurocognitive data collected for all participants as part of the IMAGE-HD study has been described in previous publications (Georgiou-Karistianis et al., 2013, in press; Gray et al., 2013).

The IMAGE-HD study was approved by the Monash University and Melbourne Health Human Research Ethics Committees. Written informed consent was obtained from each participant in accordance with the Helsinki Declaration.

MRI data acquisition

Structural and functional MR images were acquired with the Siemens Magnetom Tim Trio 3 T MRI scanner (Siemens AG, Erlangen, Germany) and a 32-channel head coil at the Murdoch Children's Research Institute (Royal Children's Hospital, Victoria, Australia). High-resolution T1-weighted images were acquired (192 slices, slice thickness of 0.9 mm, 0.8 mm 0.8 mm in-plane resolution, 320×320 matrix, TI = 900 ms, TE = 2.59 ms, TR = 1900 ms, flip angle = 9°). Diffusion weighted data were acquired using a double spin echo diffusion weighted EPI sequence (TR = 8200, TE = 89 ms, flip = 90°, 64 contiguous slices with 2 mm isotropic voxels, acquisition matrix 128×128). Diffusion-sensitizing encoding gradients were applied in 60 directions using a b value of 1200 s/mm^2, and 10 images without diffusion weighting (b = 0 s/mm2) were acquired.

MRI data processing

FMRIB's diffusion toolbox (FDT) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) was used for eddy current correction and elimination of motion artifacts. Diffusion tensors were estimated and the reconstructed tensor matrices were diagonalized to obtain eigen values (λ_1, λ_2, λ_3) for estimation of the radial diffusivity (RD) and fractional anisotropy (FA) of each voxel.

For spatial normalization of DTI data to a common standard space, an iterative normalization procedure was used (Muller et al., 2011). The FA image from each subject was first normalized to the Montreal Neurological Institute (MNI) 1 mm^3 resolution FA Map using non-linear registration (FNIRT). A study specific FA template was created by arithmetically averaging the normalized FA maps for participants from each group.