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White matter integrity in premanifest and early Huntington's disease is related to caudate loss and disease progression

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ABSTRACT

Introduction: Huntington's disease (HD) is associated with progressive loss of caudate and white matter volume and integrity. Our aim was to systematically assess interactions between these changes and genetic markers of disease progression; we are not aware of previous studies in which this has been explicitly tested.

Methods: Tract-based spatial statistics were used to assess: (a) differences between the white matter diffusion metrics (fractional anisotropy and mean diffusivity) of 17 premanifest and 19 early manifest HD gene carriers and 21 controls, and (b) the relationships between diffusion metrics, caudate and total white matter volume, and disease burden score and CAG repeat length. Caudate and total white matter volumes were quantified using FIRST and SIENAX respectively. Multiple regression analysis was used to assess which of the imaging metrics predicted disease severity in the HD subjects.

Results: Diffusion metrics were significantly altered in premanifest and early HD gene carriers in comparison with controls throughout the white matter skeleton. Correlations between diffusion and volumetric metrics and disease progression were also present. Together, caudate volume and mean white matter fractional anisotropy and mean diffusivity predicted disease burden score in the HD subjects.

Conclusions: The diffusion properties of white matter are extensively altered in HD, and are associated with markers of HD severity, and with caudate and white matter volumes. The correlation between diffusion metrics and white matter volume is stronger in HD subjects than in controls, but there is no such significant interaction for the correlation between diffusion and caudate volume: we propose that many of the changes in white matter diffusion in HD occur as a 'normal' physiological response to pathological caudate volume loss. We have defined the extent to which mean white matter fractional anisotropy, white matter volume and caudate volume are associated with disease burden score.

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1. Introduction and objectives

Huntington's disease (HD) is a devastating and incurable neurodegenerative disease caused by autosomal dominant inheritance of an expanded CAG trinucleotide repeat within the Huntingtin (*HTT*) gene (The Huntington's Disease Collaborative Research Group, 1993). Clinical disease onset is typically in late-middle age and comprises motor, cognitive and neuropsychiatric symptoms (Novak & Tabrizi, 2010). The pathological hallmark of HD is loss of the striatal medium spiny neurons (Vonsattel et al., 1985), and striatal volume loss is the earliest and most characteristic structural abnormality seen using brain imaging (Aylward et al., 1994; Tabrizi et al., 2009). As the disease progresses, histological and structural brain changes become widespread: structural imaging reveals extensive basal ganglia, cortical and white matter volume loss (Rosas et al., 2003; Tabrizi et al., 2009, 2011, 2012). Robust quantification of imaging changes is important in the development of HD biomarkers, and hence as part of the development of putative new disease-modifying therapies.

CAG repeat length can be quantified through genetic testing and accounts for 50–70% of variance in the age of onset of clinically manifest disease (Wexler et al., 2004). The relationship with manifest disease progression is less well-defined; CAG repeat length appears to be less strongly associated with clinical disease progression than with the age of disease onset (Ravina et al., 2008; Rosenblatt et al., 2006). Individuals at risk of inheriting the expanded HD gene because of their family history can elect to undergo predictive genetic testing: those who are found to carry the expanded gene on predictive testing but who do not yet have any symptoms of the disease are known as premanifest, or prodromal, HD gene carriers. Once a gene carrier develops characteristic HD motor signs, he or she is said to have manifest HD (Huntington Study Group, 1996).

Much neuroimaging research in HD has focussed on the identification of biomarkers of disease progression. Brain imaging has also shed much light on the underlying pathology of HD, and there are many imaging studies in the literature which illustrate this (Bohanna, Georgiou-Karistianis, Hannan, & Egan, 2008; Kloppel et al., 2009). Historically, much of the focus of such studies has been on grey matter volume loss, especially subcortical atrophy, but it is now clear that HD also affects white matter. Both white matter volume loss (Paulsen et al., 2006; Rosas et al., 2006; Tabrizi et al., 2009) and altered white matter diffusion metrics (Della Nave et al., 2010; Douaud et al., 2009; Dumas et al., 2012; Kloppel et al., 2008; Magnotta et al., 2009; Mascalchi et al., 2004; Muller et al., 2011; Reading et al., 2005; Rosas et al., 2010; Rosas et al., 2006; Stoffers et al., 2010; Weaver et al., 2009) have been documented in premanifest and manifest HD subjects. Diffusion metrics are used to characterise the diffusion of water molecules within tissue: fractional anisotropy is a measure of the coherence, or dispersion, of water diffusion, whereas diffusivity is a measure of the magnitude of water diffusion. Mean diffusivity is a directionally averaged measure of water diffusion. Neither white matter volume nor diffusion metrics are specific to separable biological components of the neurodegenerative process, but imaging measures of white matter volume loss indicate macroscopic tissue loss, whereas altered diffusion metrics reflect loss of microscopic tissue structure (Beaulieu, 2002; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996; Ulug, Moore, Bojko, & Zimmerman, 1999). In HD, the cellular changes underlying white matter damage are not fully understood, but might include any or all of: intrinsic axonal degeneration; loss of white matter organisation or density e.g., through inflammation; or demyelination (Rosas et al., 2006).

Altered diffusion within white matter suggestive of degeneration in this tissue has previously been shown cross-sectionally in both premanifest and HD subjects compared with controls at a group level (Della Nave et al., 2010; Douaud et al., 2009; Dumas et al., 2012; Kloppel et al., 2008; Magnotta et al., 2009; Mascalchi et al., 2004; Muller et al., 2011; Reading et al., 2005; Rosas et al., 2010; Rosas et al., 2006; Stoffers et al., 2010; Weaver et al., 2009). However, we are not aware of any studies in which a differential group effect between premanifest and manifest subjects has been shown. This was explicitly tested for in the corpus callosum by one group (Rosas et al., 2010), but, although there were differences in the results of comparisons of premanifest and manifest data respectively with control data, no significant differences were found on direct comparison of the premanifest and manifest subjects. There is also no clear consensus over the anatomical extent of changes, with changes in different regions in different studies: affected regions include, for example, striatum (Douaud et al., 2009; Dumas et al., 2012; Kloppel et al., 2008; Magnotta et al., 2009; Mascalchi et al., 2004; Rosas et al., 2006), pallidum (Douaud et al., 2009; Kloppel et al., 2008; Rosas et al., 2006), thalamus (Douaud et al., 2009; Dumas et al., 2012; Rosas et al., 2006; Stoffers et al., 2010) and cortex (Dumas et al., 2012; Magnotta et al., 2009; Reading et al., 2005; Rosas et al., 2006). Furthermore, the relationship between diffusion metrics and disease progression is not well-characterised. In manifest subjects, Della Nave et al. (2010) demonstrated an association between mean diffusivity (but not fractional anisotropy) and disease duration. In premanifest gene carriers, Magnotta et al. (2009) found regions of grey and white matter in which estimated probability of disease onset within five years was positively correlated with fractional anisotropy, regions in which it was negatively correlated with fractional anisotropy, and regions in which it was positively correlated with mean diffusivity. Findings from both of these studies were, however, limited by uncorrected statistical associations. Discrepancies also exist in the results of longitudinal studies: in one study (Weaver et al., 2009), longitudinal change in fractional anisotropy and axial diffusivity in white matter was shown over one year in a cohort of seven HD subjects compared with controls, whereas in other studies, no longitudinal change in diffusion metrics were seen. Specifically, no longitudinal change in mean diffusivity was seen over one year when tested in the caudate, putamen, thalamus and corpus callosum of 18 manifest subjects compared with controls (Sritharan et al., 2009), and no longitudinal change in MD was seen in the caudate or putamen of eight manifest HD subjects over two years (Vandenberghe, Demaerel, Dom, & Maes, 2009).

The main aim of this cross-sectional study was to examine altered white matter microstructure in premanifest and early manifest HD. The secondary aims were to investigate the relationship between diffusion metrics and volumetric and genetic measurements of disease progression in HD, and to compare those imaging metrics as predictors of disease