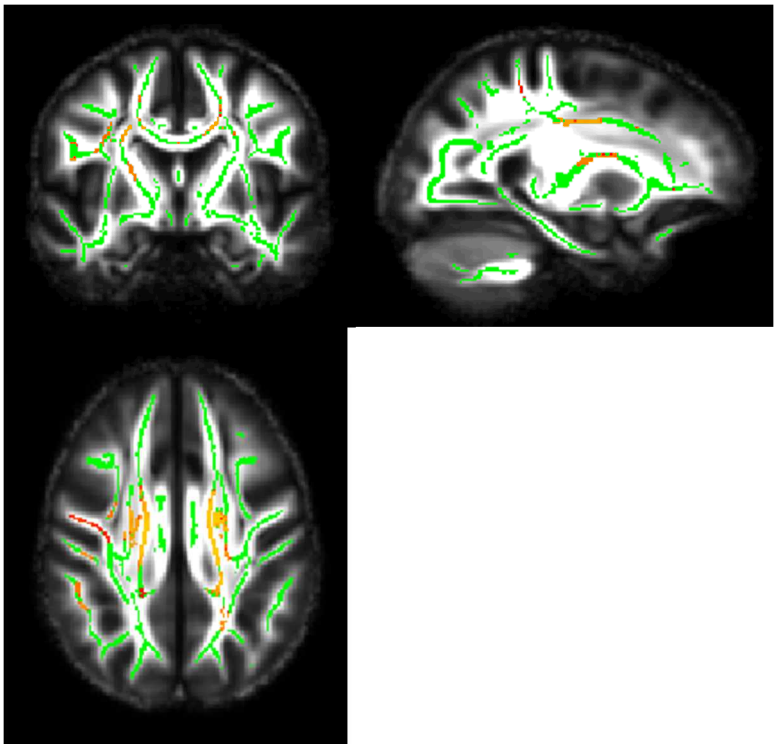
Supplementary Data

Supplementary Table 1: Tracts in which reduced FA was correlated with increased CPO; FWE-corrected threshold of p<0.05

Maximum Intensity Voxel					
x	**y**	**z**	**Voxels**	**p-value**	**White Matter tracts**
97	150	77	5585	0.006	Bilateral Callosal Body
					Bilateral Genu
					Bilateral Anterior Corona Radiata
					Left Posterior Corona Radiata
					Bilateral Superior Corona Radiata
					Left Anterior Limb of Internal Capsule
					Right Anterior Limb of Internal Capsule
					Right Superior Longitudinal Fasc.
92	67	83	315	0.038	Left Posterior Thalamic Radiation
					Left Posterior Corona Radiata
					Right Cerebral Peduncle
126	89	121	270	0.045	Unclassified
135	82	114	247	0.048	Unclassified
127	78	100	25	0.049	Right Posterior Corona Radiata

Supplementary Figure 1: Tracts in which reduced FA was correlated with increased CPO; FWE - corrected threshold of P<0.05. Results (red-yellow) are projected on a white matter skeleton (green), overlaid on a customized mean FA image.



Supplementary Methods

Participant Information

All information regarding participant recruitment, quantitative motor, cognitive and neuropsychiatric assessments has been reported previously[4].

Diffusion Imaging Acquisition

Diffusion Imaging was not originally included in the core TRACK-HD imaging acquisitions, although both the Paris and Leiden sites did independently collect diffusion data at the same time as the core scans early on in the study. When it was decided to collect diffusion data from all three European sites for the 2011 timepoint, scanning parameters were harmonised as closely as possible but in the interests of maintaining longitudinal consistency with earlier acquisitions there were inevitably some minor differences between sites.

Quality Control of Imaging Data

Track-HD implemented quality assurance procedures to ensure that scans obtained at different times in different centres using different hardware/software combinations were as comparable as possible. These included preparatory inter-scanner comparisons using phantoms and/or human volunteers.

Atrophy as a confounding variable

Direct measures of atrophy were not included as confounding variables in the analysis. Given the existing evidence it was unclear which white matter tracts would most likely be affected by both neuropsychiatric symptoms and changes in diffusivity within HD. Thus, we opted for a whole brain analysis with appropriate corrections for multiple comparison. We did not want to exclude potential effects of structural connectivity change by removing the potential effects of atrophy which form part of the HD pathology. Therefore, we chose not to include atrophy as a confounding variable. We did, however, include total intracranial volume within the analyses.

Supplementary Results

The role of site effects on neuropsychiatric measures

We investigated possible site effects for depression, irritability/aggression and apathy scores. A one-way ANOVA, shows that there were no statistically significant ($P<0.05$) site effects for any of the neuropsychiatric scores (depression: $F(2,81) = 1.421$, $p=0.248$; irritability/aggression: $F(2,81) = 0.690$, $p=0.505$; apathy: $F(2,78) = 2.514$, $p=0.088$).

The role of site effects on FA values

We investigated possible site effects on FA by examining the interaction between each neuropsychiatric score and CPO separately for each site. For depression, as CPO varied, there was an association between FA and depression scores in the Corpus Callosum for each site at a corrected threshold (London: right $p=0.08$, left $p=0.09$; Paris: right $p=0.08$, left = 0.1; Leiden: right $p=0.05$, left = 0.06). For irritability, as CPO varied, there were no such site-specific associations at a corrected level. At a much lower, uncorrected threshold there was an association between FA and irritability/aggression scores across the brain (London: $p=0.05$; Paris: $p=0.05$; Leiden: $p=0.05$). For Apathy, there was no association between FA and apathy scores at the corrected level, with the exception of a small cluster in the right posterior thalamic radiation for the London site. However, this finding was not present for either the Paris or the Leiden data separately or for the main analyses. Given the consistency of results for both the depression and irritability scores, in contrast there are no clear site effects and therefore, the results for the combined sites we believe to be robust. Furthermore, given the above findings, we have no evidence that differences in scanner type (London and Paris – Siemens; Leiden – Phillips) impacted the findings.

Relationship between FA and neuropsychiatric scores using caudate volume as a marker of disease progression

Given that the caudate is one of the regions most vulnerable to pathology in premanifest HD, we have explored the relationship between caudate volume and FA in this group. Using TBSS, we identified a significant negative correlation between fully-automated segmented caudate volume [33] and FA values, such that the lower the caudate volume, the lower the FA values. This was compatible with the findings included in the main text, which showed that as CPO increases, the lower the FA values. This was the case across the whole brain. We then explored the relationships between caudate volume and neuropsychiatric measures on FA values. However, unlike for CPO, there were no significant associations between neuropsychiatric measures and FA as caudate volume varied. Even at an uncorrected threshold, these effects were minimal. As the correlation

between CPO and caudate volume is high (r=-0.667, p=0.001) as both represent markers of disease progression. However, the difference in associations between neuropsychiatric measures and white matter microstructural changes when using CPO and caudate volume respectively, indicates that these measures can also represent different aspects of disease progression. Changes in caudate volume reflect more directly the neurodegenerative pathology associated with HD progression and it is possible that an association between caudate volume, white matter microstructural change and neuropsychiatric scores would be confounded by this. This would also be the case with both whole-brain gray and white matter volume. We, therefore, used CPO as a clinical non-morphological measure of disease progression.