Clinical Impairment in Premanifest and Early Huntington's Disease is Associated with Regionally Specific Atrophy

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Abstract: TRACK-HD is a multicentre longitudinal observational study investigating the use of clinical assessments and 3-Tesla magnetic resonance imaging as potential biomarkers for future therapeutic trials in Huntington's disease (HD). The cross-sectional data from this large well-characterized dataset provide the opportunity to improve our knowledge of how the underlying neuropathology of HD may contribute to the clinical manifestations of the disease across the spectrum of premanifest (PreHD) and early HD. Two hundred and thirty nine gene-positive subjects (120 PreHD and 119 early HD) from the TRACK-HD study were included. Using voxel-based morphometry (VBM), grey and white matter volumes were correlated with performance in four domains: quantitative motor (tongue force, metronome tapping, and gait); oculomotor [anti-saccade error rate (ASE)]; cognition (negative emotion recognition, spot the change and the University of Pennsylvania smell identification test) and neuropsychiatric measures (apathy, affect and irritability). After adjusting for esti-

mated disease severity, regionally specific associations between structural loss and task performance were found (familywise error corrected, $P < 0.05$); impairment in tongue force, metronome tapping and ASE were all associated with striatal loss. Additionally, tongue force deficits and ASE were associated with volume reduction in the occipital lobe. Impaired recognition of negative emotions was associated with volumetric reductions in the precuneus and cuneus. Our study reveals specific associations between atrophy and decline in a range of clinical modalities, demonstrating the utility of VBM correlation analysis for investigating these relationships in HD. *Hum Brain Mapp* 34:519–529, 2013.   © 2011 **Wiley Periodicals, Inc.**

Key words: TRACK-HD; magnetic resonance imaging; voxel-based morphometry

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion on chromosome 4 [The Huntington's Disease Collaborative Research Group, 1993] and consequently can be identified before symptom onset by predictive genetic testing. The clinical characteristics are progressive motor dysfunction, cognitive decline and psychiatric disturbance. Formal diagnosis is based on the presence of unequivocal and otherwise unexplained movement disorder [Huntington's Disease Study Group, 1996].

There is now a wealth of evidence showing subtle functional deficits occur many years prior to clinical diagnosis. Recent studies describe impairment in motor and cognitive function up to 15 years before predicted disease onset [Biglan et al., 2009; Duff et al., 2010; Paulsen et al., 2008; Stout et al., 2011; Tabrizi et al., 2009, 2011]. Impaired oculomotor function has been reported in premanifest gene carriers (PreHD) [Blekher et al., 2006; Golding et al., 2006; Hicks et al., 2008; Lasker and Zee, 1997; Tabrizi et al., 2009] as have deficits in emotion recognition [Johnson et al., 2007; Tabrizi et al., 2009] and neuropsychiatric disturbances [Berrios et al., 2002; Julien et al., 2007; Tabrizi et al., 2009]. Structural neuroimaging studies reveal macroscopic effects of the underlying neuropathology with striatal volume loss [Aylward et al., 1997, 2004, 2010; Hobbs et al., 2009; Tabrizi et al., 2009, 2011] and global brain atrophy [Henley et al., 2009; Squitieri et al., 2009; Tabrizi et al., 2009, 2011; Thieben et al., 2002] as well as cortical thinning [Nopoulos et al., 2010; Rosas et al., 2002, 2005; Tabrizi et al., 2009] evident in both manifest and premanifest cohorts. Recent work has demonstrated a close association between structural loss and clinical phenotype [Henley et al., 2008; Rosas et al., 2005, 2008].

Studying incipient functional deficits and the distribution of structural changes in individuals destined to develop HD and in the early manifest stages increases our understanding of how the disease progresses and how underlying neuropathology may contribute to the clinical manifestations of HD. At this early stage deficits are specific and isolated, unlike in the advanced stages where structural loss and functional impairment become increasingly global.

TRACK-HD is a large prospective multicentre longitudinal observational study, with the aim of identifying potential biomarkers for future use in disease-modifying clinical trials, which has been described in detail previously [Tabrizi et al., 2009, 2011]. We sought to examine the relationship between these clinical deficits and regional atrophy across the spectrum of premanifest to early Huntington's disease.

METHODS

Subjects

All subjects were recruited as part of the TRACK-HD study [Tabrizi et al., 2009] which included 120 PreHD and 123 early HD subjects. Assessments were performed at four centres: the Department of Neurology at Leiden University Medical Centre, the National Hospital for Neurology and Neurosurgery, London, the Department of Medical Genetics at the University of British Columbia, Vancouver, and the Department of Genetics and Cytogenetics at the Hôpital de la Salpêtrière-Université Pierre and Marie Curie, Paris. Clinical assessment was standardized across sites and performed using the Unified Huntington's Disease Rating Scale UHDRS-99, medical and psychiatric history, current medications, HD history, clinical motor scores, portions of the cognitive component and functional capacity. PreHD subjects required a disease-burden score of >250 [Penney et al., 1997] and a total motor score of ≤5 in the UHDRS motor assessment indicating lack of significant motor signs. Early HD subjects included HD Stage I and HD Stage II, based on a total functional capacity score of >7 [Shoulson and Fahn, 1979]. The study was approved by the local ethical committees and written informed consent was obtained from each subject according to the Declaration of Helsinki.

Image Acquisition and Processing

The 3T MRI data were acquired according to a standardized T1-weighted protocol developed for this study [Tabrizi et al., 2009]. Details are provided in the Supporting Information. Four early HD subjects had scans which were unsuitable for VBM analysis due to poor scan quality resulting in 239 gene-positive subjects (120 PreHD and 119 early HD) being included in the study. Total intracranial volume was calculated using the MIDAS software [Freeborough et al., 1997] following a semiautomated protocol previously described [Whitwell et al., 2001]. VBM was

performed using Statistical Parametric Mapping version 5 (www.fil.ion.ucl.ac.uk/spm). Initial tissue classification was performed using the unified segmentation process with rigid alignment. DARTEL (diffeomorphic anatomical registration using exponentiated lie algebra) [Ashburner, 2007] was used to create a study-specific template. The initial tissue segmentations were spatially normalized using high dimensional warping onto the template then modulated to account for volume change during the normalisation process. Because of the improved registration accuracy of DARTEL and to improve anatomical localisation, we smoothed with a relatively small kernel of 4-mm full width at half maximum. All images were visually inspected blind to diagnosis to ensure segmentation accuracy.

Assessments

A large number of assessments were performed on the TRACK-HD cohort; here we report on a subset from each of the modalities that showed the most significant cross-sectional differences at baseline [Tabrizi et al., 2009]. Additional details on these assessments are provided in the Supporting Information.

Quantitative motor

Isometric force during sustained tongue protrusion was recorded using a force transducer [Reilmann et al., 2010]. The logarithm of the coefficient of variation in tongue force was used in our assessment. The same force transducer system was used for the metronome tapping task, which involved subjects first tapping their index finger in response to tones produced by a metronome and then continuing to tap at this rhythm without further cues [Bechtel et al., 2010]. We measured the precision of the taps produced without cues by the nondominant hand, which was defined as 1/SD of the deviation of taps from the training tap rate (reported in [Tabrizi et al., 2009] and referred to as Delta-MTI in [Bechtel et al., 2010]). For gait, stride length variability was assessed during normal speed walking using a GAITrite system (CIR Systems, Havertown, PA) [Rao et al., 2008]. The log of the coefficient of variation in stride length was calculated.

Oculomotor

Horizontal eye position was recorded using the Saccadometer Advanced (Ober Consulting, Poznan, Poland) during a random, centrally cued mixed pro/antisaccade task [Hicks et al., 2008] and the rate of errors in antisaccade component was calculated.

Cognitive

Recognition of negative emotions (sadness, anger, fear, or disgust) was assessed using a subset of the Ekman and Friesen facial stimuli [Ekman and Friesen, 1976]. Spot the change was designed to assess visual working memory and involved participants identifying changes in colored squares presented on a computer screen and the number correct was adjusted for guessing. An abbreviated (20-item) version of the University of Pennsylvania smell identification test (UPSIT; Sensonics, Haddon Heights, NJ), was used to assess recognition of common odors.

Neuropsychiatric

A brief semistructured interview that was a shortened form of the problem behaviors assessment (PBA-s) [Craufurd et al., 2001] was administered by raters trained to meet reliability thresholds. Apathy, irritability, and affect scores were calculated as the frequency × severity of each symptom over the past month and the square root of the scores was entered into the model.

Statistical Analysis

All gene-positive carriers (PreHD and early HD) were included in the correlation analysis. For the metronome tapping task, only right-handed subjects were included. See Supporting Information Table I for details of nonmissing values for each assessment.

Correlations between grey-matter (GM) or white-matter (WM) volumes and performance on the various assessments were examined using linear regression models within SPM5. Age, gender, study site, education, total intracranial volume, CAG repeat length and disease-burden score [Penney et al., 1997] were included as covariates in the model. CAG repeat length and disease-burden score were included to adjust for overall disease severity to identify more specific relationships between task performance and tissue loss. Age and CAG repeat length are known to influence the onset and trajectory of the disease and disease-burden score was included to represent an interaction between these two terms.

An explicit binary mask was used for analysis, generated using the optimal thresholding technique described by Ridgway et al. [2009]. Results were corrected for multiple comparisons using familywise error at the $P < 0.05$ level. Reverse contrasts were examined to investigate whether there was any evidence of greater GM or WM volume associated with task impairment. Anatomical localisation was performed in consultation with a trained neuroradiologist (HH) using xjview (http://www.alivelearn.net/xjview/).

RESULTS

Subject Demographics

The characteristics of the PreHD and early HD cohort are shown in Table I. Details of medication usage are provided in Supporting Information Table II. As expected due to the progressive nature of the disease, the mean ages of

TABLE I. Subject demographics

	PreHD ($n = 120$)	Early HD ($n = 119$)
Age (years)	40.8[a] (8.9)	48.5[a] (9.9)
Gender (M:F)	66:54	64:55
CAG length	43.1 (2.4)	43.7 (3.0)
UHDRS total motor score	2.5[a] (1.6)	23.6[a] (10.8)
Tongue force (log coefficient of variation)	3.6[a] (0.5)	4.4[a] (0.6)
Metronome tapping precision (1/SD deviation from taps)	32.9[a] (11.9)	16.2[a] (10.2)
Gait (log coefficient of variation)	1.0[a] (0.3)	1.3[a] (0.4)
Anti-saccade error rate (%)	33.3[a] (19.6)	58.0[a] (25.3)
Recognition of negative emotions (no correct/50)	23.4[a] (5.7)	16.7[a] (6.2)
Spot the change 5 K score (no correct, corrected for guessing)	2.8[a] (1.3)	1.6[a] (1.3)
UPSIT (no correct/20)	16.5[a] (2.6)	13.6[a] (3.2)
PBA Apathy Score (frequency × severity)	0.5[a] (0.9)	1.1[a] (1.2)
PBA irritability score (frequency × severity)	1.5[b] (1.3)	2.0[b] (1.3)
PBA affect score (frequency × severity)	2.0 (1.4)	2.1 (1.3)

Mean (standard deviation).
UPSIT = University of Pennsylvania Smell Identification Test; PBA = Problem Behaviours Assessment.
[a]PreHD significantly different from early HD $P < 0.0001$.
[b]PreHD significantly different from early HD $P < 0.001$.

these two groups were significantly different ($P < 0.001$). There were no significant differences in mean CAG repeat length ($P = 0.09$). With the exception of the affect score ($P = 0.38$), all assessments showed significant impairment in the early HD compared with the PreHD group ($P < 0.001$).

Quantitative Motor

Tongue Force

There was a strong correlation between tongue force variability and GM reduction in the striatum bilaterally and in the right precentral gyrus which included sensory and motor regions (Fig. 1, Supporting Information Fig. 1 and Table II). There was also involvement of the right cuneus and the precuneus bilaterally. Increased tongue force variability was also associated with WM reductions in the left and right occipital lobes as well as the splenium of the corpus callosum and the internal capsule.

Finger tapping

Reduced precision on metronome tapping was associated with bilateral reduction of GM throughout the striatum and WM bilaterally in the internal capsule and in the right external capsule (Fig. 2, Supporting Information Fig. 2 and Table II).

Gait

Significant associations between increased variability in stride and structural loss were localised to a small area of GM in the left hippocampus (Supporting Information Fig. 3 and Supporting Information Table III).

Oculomotor

Increased antisaccade error rate was associated with bilateral GM reduction in the striatum as well as localised regions of the left lateral occipital lobe, right superior temporal and right inferior frontal gyri (Fig. 3, Supporting Information Fig. 4 and Table II). Increased error rates were also associated with WM reduction in the internal capsules bilaterally and the left external capsule as well as the parieto-occipital and frontostriatal regions.

Cognitive

Emotion

Poor performance on the negative emotion recognition task correlated with GM reduction in the right cuneus and precuneus, the left precentral gyrus close to the sensorimotor area and bilaterally in the lingual gyri (Fig. 4, Supporting Information Fig. 5 and Table II). Impairment of negative emotion recognition correlated with WM reduction in the left external capsule and the right parietal area.

Spot the Change

Increased error on the spot the change task was related to an isolated GM region in the left middle frontal gyrus as well as single voxels in the right inferior parietal lobe and the right fusiform. Associations with WM reduction were seen in the genu of the corpus callosum (Supporting Information Fig. 6 and Supporting Information Table III).

UPSIT

There was a correlation between impairment in smell identification and reduced GM volume of the superior right hippocampus and the left insula (Supporting

TABLE II. Anatomical regions of correlations across the whole cohort

		Anatomical location	Cluster size	T score	P value (FWE corrected)
Tongue force	GM	R caudate	1007	7.27	<0.001
		R precentral gyrus	385	6.93	<0.001
		L caudate	738	6.72	<0.001
		R cuneus	115	6.46	<0.001
		R precuneus	295	6.43	<0.001
		L precuneus	90	6.09	<0.001
	WM	R occipital lobe	27	5.46	0.003
		L occipital lobe	43	5.38	0.004
		R internal capsule	36	5.38	0.004
		Splenium corpus callosum	31	5.05	0.017
		L frontal lobe	3	5.03	0.018
Metronome tapping precision	GM	L putamen	754	6.65	<0.001
		R putamen	905	6.59	<0.001
	WM	R internal capsule	272	6.11	<0.001
		L internal capsule	435	5.92	<0.001
		R external capsule	15	5.37	0.005
Antisaccade error rate	GM	L caudate	1179	7.02	<0.001
		R caudate	870	6.99	<0.001
		L lateral occipital gyrus	12	5.26	0.017
		R superior temporal gyrus	4	5.18	0.023
		L putamen	3	5.08	0.036
		R inferior frontal gyrus	2	5.03	0.043
	WM	L external capsule	78	5.98	<0.001
		R internal capsule	387	5.68	0.001
		L internal capsule	234	5.67	0.001
		R occipital lobe	71	5.54	0.002
		L parietal lobe	68	5.34	0.005
		R frontal lobe	23	5.15	0.011
Recognition of negative emotions	GM	L precentral gyrus	16	5.26	0.018
		R precuneus	8	5.26	0.018
		R cuneus	23	5.25	0.019
		L lingual gyrus	4	5.24	0.019
		R lingual gyrus	5	5.19	0.024
	WM	L external capsule	61	5.52	0.002
		R parietal lobe	42	5.17	0.011
		R superior frontal lobe	17	5.15	0.011
		R inferior parietal lobe	40	5.10	0.013

Results shown are the most significant local maxima more than 8-mm apart with a familywise error corrected P value of <0.05.

Information Fig. 7 and Supporting Information Table III) and reduced WM volume bilaterally in the temporal stems and the right parietal and frontal regions.

Neuropsychiatric

There was little evidence of associations between the neuropsychiatric variables examined here and volume reduction with the exception of a single voxel in the WM of the right lingual gyrus (Supporting Information Fig. 8 and Supporting Information Table III).

Reverse contrasts

There were no regions of significantly larger GM or WM volumes associated with impairment on any of the assessments.

DISCUSSION

We present new findings showing how clinical impairment in premanifest and early HD associates with regionally specific GM and WM atrophy across three assessment modalities, namely quantitative motor, oculomotor, and emotion recognition. In contrast, there was little evidence relating neuropsychiatric abnormalities to structural brain deficits.

Deficits in tongue protrusion force coordination were associated with bilateral loss in the striatal areas as would be expected from a motor-dependent task. In addition, there was involvement superiorly of GM including both the sensory and motor areas. It is possible that sensory feedback via the tongue itself is also impaired in HD, which is supported by evidence from a recent diffusion tensor imaging (DTI) study reporting an association
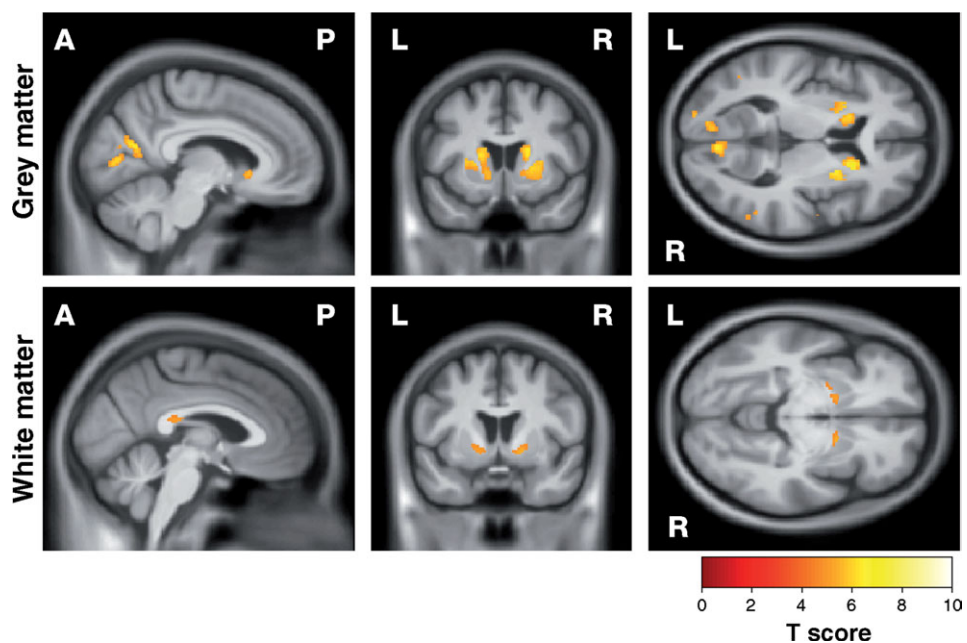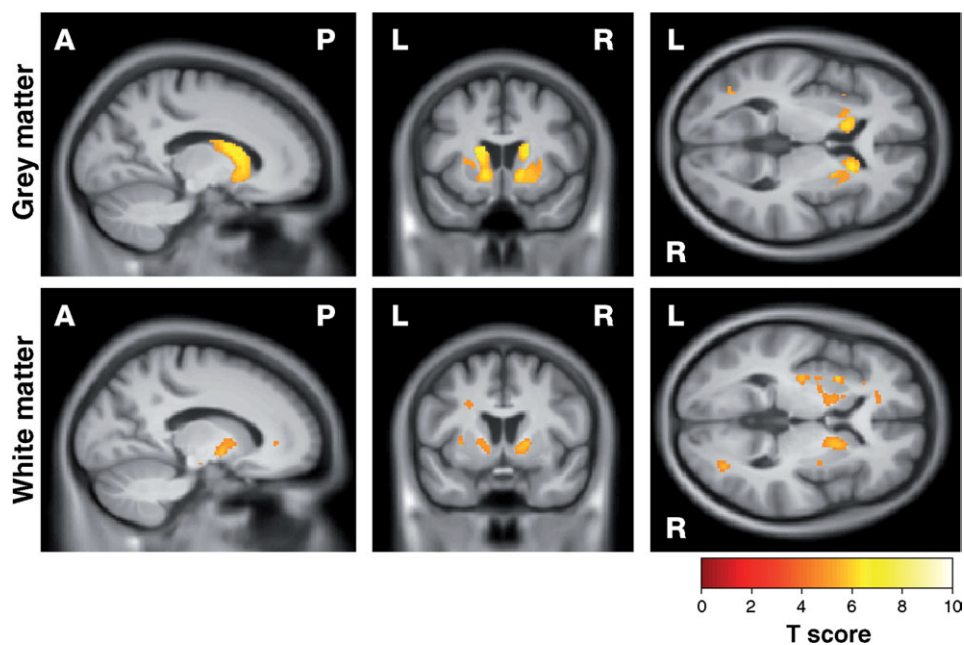
Figure 1.
Statistical parametric map (SPM) showing correlations between increased variability in tongue force and reduction in (top) GM and (bottom) WM. Results are shown overlaid on a mean customized template at $P < 0.05$, corrected for multiple comparisons using familywise error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
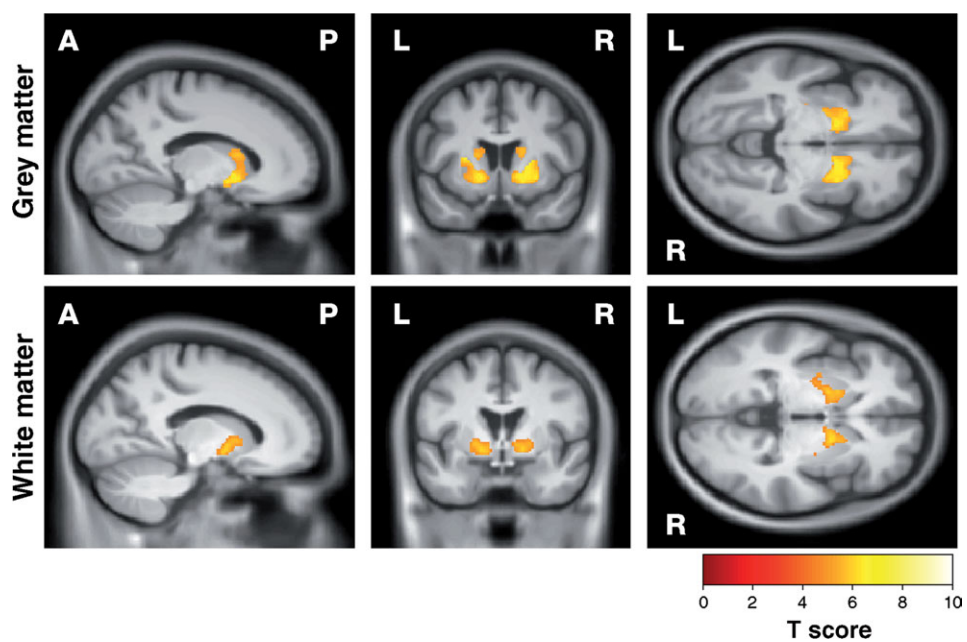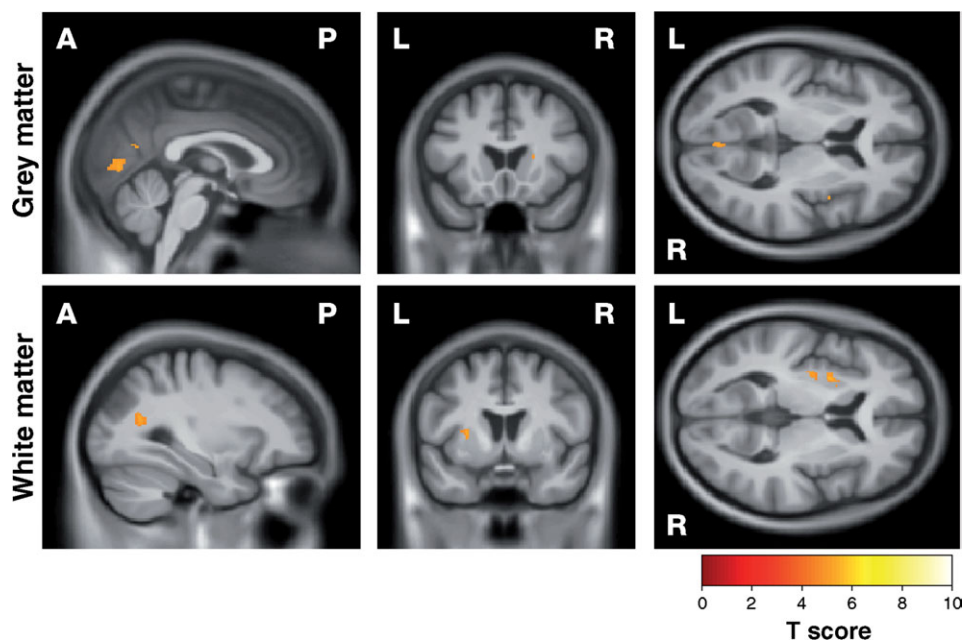

Figure 2.
SPM showing correlations between decreased precision in metronome tapping and reduction in (top) GM and (bottom) WM. Results are shown overlaid on a mean customised template at $P < 0.05$, corrected for multiple comparisons using familywise error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

SPM showing correlations between increased anti-saccade error rate and reduction in (top) GM and (bottom) WM. Results are shown overlaid on a mean customised template at $P < 0.05$, corrected for multiple comparisons using familywise error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 4.

SPM showing correlations between decrease in recognition of negative emotion and reduction in (top) GM and (bottom) WM. Results are shown overlaid on a mean customised template at $P < 0.05$, corrected for multiple comparisons using familywise error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

between reduced WM integrity in this region and deficits in tongue force coordination [Dumas et al., 2011]. This task is also heavily reliant on visual feedback as it allows subjects to monitor their performance and the association with the occipital lobe supports the suggestion that visual functions are also impaired in HD. This is consistent with a recent study demonstrating an association between visual motor impairment and cortical thinning in the occipital lobe [Rosas et al., 2008].

A reduction in precision of metronome tapping was strongly associated with bilateral caudate and putaminal volume reduction as well as the associated striatal WM, consistent with previous work using this dataset [Bechtel et al., 2010]. This is in contrast to the findings of Dumas et al. who report no association between tapping and DTI-derived measures of WM degradation in this region, also using the TRACK dataset [Dumas et al., 2011]. However, Dumas et al. used a smaller subset of the TRACK cohort so may not have had sufficient power to detect this effect. Methodological differences such as the different properties examined by DTI compared with structural MRI, plus the fact that the study did not adjust for overall disease severity whereas our study did, may also explain this apparent discrepancy. In addition to motor demands, metronome tapping is heavily reliant on time perception. Previous work has suggested that the basal ganglia play an important role in time perception at the sub-second level [Wiener et al., 2010] and the striatal beat frequency model suggests that the striatum contributes to an "internal clock" which is able to monitor the similarity between the current time interval and that previously encountered [Matell and Meck, 2004]. Our findings are supportive of these studies implicating the striatum in the perception of time.

We found a strong association between increased anti-saccade error rates and bilateral loss of the striatum accompanied by WM reduction in the external and internal capsules. There was also a correlation with reduction of GM and WM in the occipital and frontal lobes. This task involves both inhibition of a reflexive response towards a stimulus and a voluntary saccade away from it and the importance of the connection between the frontal eye fields and the caudate in voluntary saccades has been described previously [Ettinger et al., 2008; Kloppel et al., 2008]. The association with the occipital lobe suggests that deficits in more fundamental basic visual processing skills may also underlie impairment on this task.

Impaired recognition of negative facial emotions correlated with atrophy of the cuneus and the lingual region of the occipital lobe, which is unsurprising in a task requiring processing of visual stimuli. In contrast to a previous study by Henley et al. [2008], but in agreement with another report [Johnson et al., 2007], we found no significant association between negative emotion recognition and striatal volume. Our study differed in design from that of Henley et al as we used composite scores of negative emotions. Furthermore, adjusting for disease severity may have compensated for general disease-related striatal

change, improving the specificity of the identified associations. Further examination of separate negative emotions may provide more information about specific associations between brain anatomy and identification of emotional stimuli.

Our findings are in agreement with other studies identifying correlations between structural change and functional impairment [Bechtel et al., 2010; Biglan et al., 2009; Bohanna et al., 2011; Dumas et al., 2011]. Despite the robust associations discussed above, our VBM analysis did not detect associations between atrophy and impairment in other domains known to be affected in premanifest and early HD, namely gait, spot the change, UPSIT, or any of the neuropsychiatric measures. It is possible that there are certain characteristics of these assessments which make it more difficult to detect such associations. For example, performance can fluctuate greatly and may be more impacted by external factors than other assessments in this study. Many of the Pre-HD subjects showed floor effects in the neuropsychiatric assessments; in addition the range of values in these measures was small, hence there may have been insufficient power to detect a correlation. Furthermore, a large proportion of the subjects were being treated for neuropsychiatric disorders such as depression so it may be that the true underlying psychopathology is being masked by medication and is not reflected in the variables examined here. Our neuropsychiatric results are supported by two other studies who report no association between the Beck depression inventory and DTI-derived measures of structural integrity [Bohanna et al., 2011; Dumas et al., 2011] and a study by Starkstein et al. who found no association between atrophy and apathy in Alzheimer's disease but showed a correlation with WM hyperintensities [Starkstein et al., 2009]. It is also possible that deficits in these domains are the result of more subtle early neuronal dysfunction prior to the widespread loss of tissue and hence would not have been detectable with VBM. Further work with other imaging modalities in HD such as DTI, functional MRI or FDG-PET may shed light on the underlying mechanism behind loss of function; these techniques have already proved sensitive at detecting early functional deficits prior to clinical onset [Kloppel et al., 2009; Bohanna et al., 2011].

A strength of our study is the fact that we have taken into account the estimated pathological burden for each subject. This may in part explain discrepancies with previous work [Bohanna et al., 2011; Henley et al., 2008; Rosas et al., 2008]. Clearly, all subjects with manifest disease display atrophy and impairment on a variety of tasks and this needs to be taken into account when looking for specific associations, especially with a cross-sectional analysis. We included not only age and CAG repeat length, but disease burden [Penney et al., 1997] which acts as an interaction term between these two factors. The differential associations we describe for each task suggest that we are not merely detecting global disease effects but specific links between clinical impairment and neuroanatomy. Another strength is

that we combine the whole gene-positive group, negating the need to apply an arbitrary cutoff that defines disease onset. This allows us to examine a range of disease severities from the earliest possible signs of impairment. Also, by using an automated whole-brain technique such as VBM we did not need to make any a priori assumptions about where associations were expected.

One limitation of our study is that we infer functional associations on the basis of structural data; an association between impairment on a particular task and structural loss does not prove causality. Other techniques such as functional imaging may offer more direct evidence of a link between task performance and neuronal functional impairment. However, acquiring functional data on a large cohort is problematic due to difficulty in ensuring consistency across sites and it is nevertheless likely that neuronal death and structural loss underlie much of the clinical impairment apparent in premanifest and early stage HD. Finally, whilst we assume that VBM is detecting disease-related volume loss, it is possible that these changes may also reflect pathological changes in signal intensity. Nevertheless, previous volumetry work published on this cohort has demonstrated significant volume loss in both the premanifest and early HD subjects, particularly in the striatal region [Tabrizi et al., 2009], suggesting that VBM is indeed detecting this prominent atrophy, supportive of our conclusions here.

We have demonstrated that clinical impairment in a number of domains is associated with atrophy in both GM and WM, including extra-striatal regions. The impairments seen in HD are often explained as consequences of atrophy in the striatum, and associated frontostriatal connections. It is clear from our work that atrophy in these areas is indeed associated with a range of impairments. However there is increasing evidence that other regions such as the occipital lobe are undergoing early structural change [Lange et al., 1976; Rosas et al., 2005; Tabrizi et al., 2009]. Our findings suggest that low-level visuospatial processing deficits may also contribute to the pattern of performance in HD. This has implications both for our conceptualization of the tasks used (e.g., visuospatial skills are often required in tasks that are purported to measure other cognitive domains), and to further our understanding of the difficulties experienced by those with HD. This may be an important area for further detailed research. The TRACK-HD cohort are being followed longitudinally allowing detailed definitions of the patterns of progressive atrophy and associated clinical disease progression in PreHD and early HD.

In summary, our study has revealed new and specific associations between atrophy and clinical impairment across the spectrum of premanifest and early stage HD. Such detailed studies are important for a number of reasons: (a) they yield insights into anatomical regions underlying some of the earliest functional deficits that can be measured and may help us to understand some of the heterogeneity inherent in the manifestation of HD; (b) if imaging is to be useful as a biomarker of disease progression for future clinical trials, we need to better understand the functional correlates of brain atrophy and (c) disease-modifying treatments aimed at restoring function (such as neural transplantation and mutant-huntingtin-lowering therapies) in specific brain regions in HD rely on a detailed understanding of the regional functionality of these areas in the progression of the disease. This study demonstrates the utility of VBM correlation analysis for investigating associations between structural loss and clinical manifestation in Huntington's disease.

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