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Lora Minkova[a,b,c,*], Sarah Gregory[d], Rachael I. Scahill[e], Ahmed Abdulkadir[f,g], Christoph P. Kaller[b,h,i], Jessica Peter[a,g], Jeffrey D. Long[j,k], Julie C. Stout[l], Ralf Reilmann[m,n,o], Raymund A. Roos[p], Alexandra Durr[q], Blair R. Leavitt[r], Sarah J. Tabrizi[e], Stefan Klöppel[a,g], TRACK-HD Investigators

[a] Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Freiburg, Germany
[b] Freiburg Brain Imaging Center, Medical Center – University of Freiburg, Germany
[c] Department of Psychology, Laboratory for Biological and Personality Psychology, University of Freiburg, Freiburg, Germany
[d] Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK
[e] Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, UK
[f] Department of Computer Science, University of Freiburg, Freiburg, Germany
[g] University Hospital of Old Age Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland
[h] Department of Neurology, Medical Center – University of Freiburg, Freiburg, Germany
[i] BrainLinks-BrainTools Cluster of Excellence, University of Freiburg, Freiburg, Germany
[j] Department of Psychiatry, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA
[k] Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, IA, USA
[l] School of Psychology and Psychiatry, Monash University, Victoria, Australia
[m] George-Huntington-Institute, Münster, Germany
[n] Department of Radiology, University of Münster, Münster, Germany
[o] Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
[p] Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands
[q] APHP Department of Genetics, ICM (Brain and Spine Institute) Pitié-Salpêtrière University Hospital Paris, France
[r] Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, Canada

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ABSTRACT

Huntington's disease (HD) is a progressive neurodegenerative disorder that can be genetically confirmed with certainty decades before clinical onset. This allows the investigation of functional and structural changes in HD many years prior to disease onset, which may reveal important mechanistic insights into brain function, structure and organization in general. While regional atrophy is present at early stages of HD, it is still unclear if both hemispheres are equally affected by neurodegeneration and how the extent of asymmetry affects domain-specific functional decline. Here, we used whole-brain voxel-based analysis to investigate cross-sectional and longitudinal hemispheric asymmetries in grey matter (GM) volume in 56 manifest HD (mHD), 83 pre-manifest HD (preHD), and 80 healthy controls (HC). Furthermore, a regression analysis was used to assess the relationship between neuroanatomical asymmetries and decline in motor and cognitive measures across the disease spectrum. The cross-sectional analysis showed striatal leftward-biased GM atrophy in mHD, but not in preHD, relative to HC. Longitudinally, no net 36-month change in GM asymmetries was found in any of the groups. In the regression analysis, HD-related decline in quantitative-motor (Q-Motor) performance was linked to lower GM volume in the left superior parietal cortex. These findings suggest a stronger disease effect targeting the left hemisphere, especially in those with declining motor performance. This effect did not change over a period of three years and may indicate a compensatory role of the right hemisphere in line with recent functional imaging studies.

1. Introduction

Asymmetry is an inherent property of the human brain and has been confirmed in terms of both structure and function (Toga and Thompson, 2003). Variation in the neuroanatomical and functional organization between the two brain hemispheres may arise from myriad different, often interdependent factors, including, but not limited to, development, plasticity, and pathology (Toga and Thompson, 2003). In the context of neurodegeneration, it is highly probable that disease-specific processes would interact with the asymmetries of the healthy brain, leading to either attenuated or increased lateralization. This has also raised the question of whether disease progression equally affects both brain hemispheres. In Alzheimer's disease (AD), for instance, neuronal loss appears to progress faster in the left hemisphere than in the right (Thompson et al., 2003; Thompson et al., 2001; Wachinger et al., 2016), suggesting a higher left-hemisphere susceptibility to neurodegeneration. However, others have reported greater cortical atrophy in the right, rather than the left, hemisphere in mild cognitive impairment, a pre-dementia stage of AD (Apostolova et al., 2007), which might indicate stage-dependent differences in neuronal loss.

Similarly, the presence and progression of structural asymmetries in Huntington's disease (HD) are still unclear. HD is a neurodegenerative disorder that can be genetically confirmed decades before formal clinical diagnosis of motor onset (The Huntington's Disease Collaborative Research Group, 1993). HD may serve as a model neurodegenerative disorder and has the potential to advance our general understanding of brain function and structure, as well as brain reorganization in the presence of neurodegeneration. In HD, progressive regional brain atrophy occurs well in advance of functional deficits at the preclinical stage of disease (preHD) and continues steadily after manifestation of first motor symptoms (mHD) (Ross et al., 2014). However, it remains unclear whether neurodegeneration equally affects both cerebral hemispheres across all stages of the disease. A volume-based meta-analysis of previously published voxel-based morphometry (VBM) studies found converging evidence of left-hemisphere lateralization of GM loss in preHD prior to bilateralization at the clinical stage (Lambrecq et al., 2013). However, just one cross-sectional study has explicitly addressed brain asymmetry in HD, reporting bilateral GM loss in preHD followed by left lateralization at later disease stages (Mühlau et al., 2007). This study only included a very small sample of preHD participants (n = 9), leading to inconclusive results in terms of disease stage-specific differences across the HD continuum. In a new VBM-based meta-analysis, we also found converging evidence for more pronounced atrophy of the left putamen in HD (Minkova et al., 2017), although the number of studies analyzed was insufficient to investigate the effect across different stages of HD.

In the present study, we systematically assessed disease stage-specific differences in lateralization of GM atrophy in a large sample of both pre-symptomatic (n = 83) and early stage (n = 56) HD mutation gene-carriers, relative to healthy controls (n = 80). The analysis was conducted following previous recommendations for whole-brain VBM-based asymmetry analyses (Kurth et al., 2015). Furthermore, we investigated whether asymmetries in GM atrophy changed over three consecutive years. Finally, we sought to assess the link between functional decline and GM asymmetries in HD using regression analyses

with several motor and cognitive measures, selected based on previous reports (Tabrizi et al., 2013). We hypothesized that GM lateralization would be influenced by overall disease burden and may contribute to the complex clinical phenotype and functional decline observed with disease progression. More specifically, we expected to observe more pronounced left-hemisphere vulnerability to neurodegeneration, especially in individuals closer to disease onset, which would be linked to decline in cognitive and motor performance over time. Insights into the patterns of hemispheric GM lateralization across the whole HD spectrum may provide valuable information in the context of disease-specific and compensatory mechanisms in HD and may be used to inform future interventional studies.

2. Methods

2.1. Participants

Participants were recruited at four different centers (London, Paris, Vancouver, and Leiden) over four consecutive years (2008–2012) as part of the TRACK-HD multi-center study (Tabrizi et al., 2013, Tabrizi et al., 2012, Tabrizi et al., 2011, Tabrizi et al., 2009). A total of 366 participants were initially enrolled in the TRACK-HD study at visit 1 (i.e., baseline), of which 298 completed the 36-month follow-up. We included only participants with a complete neuroimaging dataset (i.e., a T1 scan acquired annually over four years) and excluded 44 individuals with missing data. Another 35 participants were excluded because of handedness (8 ambidextrous and 27 left-handers), since our study focused on brain asymmetries and we sought to avoid the potential confounds due to handedness. Thus, the final sample comprised a total of 219 right-handed participants.

Each participant belonged to one of three groups: 56 mHD patients with a clinical motor diagnosis, 83 preHD individuals without motor symptoms but carrying the mutant huntingtin gene, and 80 healthy controls (HC), who were age- and gender-matched to the combined HD gene-carrier group. Disease status was assessed based on the Unified Huntington's Disease Rating Scale (UHDRS-99), as reported at first visit (Tabrizi et al., 2009). Table 1 provides a summary of demographic and clinical data. All participants were analyzed according to their group membership and age at first visit. No statistical differences were found in gender and education among the three groups. In terms of age, preHD were on average younger than mHD (p < 0.001). To control for potential confounding effects, age, gender, and site were included as covariates in all analyses.

The study was approved by the local ethics committees and all participants gave written informed consent according to the Declaration of Helsinki prior to participation.

2.2. Cognitive and motor assessment

Participants completed a comprehensive battery of cognitive and motor tests at baseline as well as at 12-, 24- and 36-month follow-up visits. A full description of procedures and clinical outcomes is provided elsewhere (Tabrizi et al., 2013, Tabrizi et al., 2012, Tabrizi et al., 2011, Tabrizi et al., 2009). Only pre-selected cognitive and quantitative motor (Q-Motor) measures that previously showed the highest rates of decline

Table 1
Sample characteristics.

	HC (n = 80)	preHD (n = 83)	mHD (n = 56)	Sig.
Age at baseline (years)	45.5 ± 20.1 (23–63)	41.2 ± 9.1 (19–64)	48.0 ± 10.0 (23–64)	< 0.001
Sex (female/male)	48/32	41/42	30/26	0.062
Education (median, range)	4 (2–6)	4 (2–6)	4 (2–6)	0.891
CAG repeat length	–	43.0 ± 2.4 (39–50)	43.8 ± 3.4 (39–59)	< 0.001
Disease burden score	–	291 ± 49 (171–409)	374 ± 82 (156–566)	< 0.001
Adjusted net 36-month change in:				
Symbol digit modality test	–	6.04 ± 0.61	− 8.78 ± 0.73	< 0.001
Indirect circle tracing	–	0.16 ± 0.02	− 0.24 ± 0.03	< 0.001
Q-motor speeded tapping	–	− 0.35 ± 0.03	0.52 ± 0.05	< 0.001
Q-motor grip force	–	− 0.33 ± 0.26	4.93 ± 0.64	< 0.001

The italic figures denote p values of t-tests (preHD vs. mHD). Significance in age was tested using ANOVA, which significance in sex was assessed using a chi-square test.

at 36 months were used for the subsequent analyses (Tabrizi et al., 2013). These included the following cognitive measures: symbol digit modality test (SDMT; number of correct responses) and the indirect circle tracing test (annulus length in log cm). Additionally, speeded tapping (the log-transformed variability in inter-onset interval) and grip force variability (log-transformed) of the non-dominant hand were used as Q-Motor measures. Performance decline was defined by the adjusted net 36-month change in cognitive (SDMT and circle tracing) and Q-Motor (tapping and grip force) measures, with higher values in cognitive scores indicating improvement and higher motor scores, indicating greater deterioration. Change in scores was estimated using a linear mixed-effects model including age, sex, and site as covariates. The analysis was implemented in the *lme4* package (Bates et al., 2015) for the *R* computing program (R Core Team, 2016) and was conducted for HD mutation gene-carriers only, since we were interested in the predictive value of disease-specific asymmetries for decline in performance.

2.3. MRI acquisition

Scanning was performed on 3 Tesla whole-body scanners: Siemens MAGNETOM TimTrio MR (Paris and London) and Phillips Achieva (Vancouver and Leiden). High-resolution three-dimensional T1-weighted structural scans were acquired for all participants with a magnetization-prepared rapid gradient echo (MP-RAGE) sequence and using standardized protocols, specifically developed for this multi-center study, with the following parameters for the two scanner types, respectively (Siemens/Philips): TR = 2200 ms/7.7 ms; TE = 2.2 ms/3.5 ms; FA = 10°/8°, FOV = 28 cm/24 cm, matrix size of 256 × 256 × 208/224 × 224 × 164, and slice thickness of 1.0 mm, with no inter-slice gap.

2.4. MRI data preprocessing

Structural MRI data preprocessing was performed using CAT12 v.953 (http://dbm.neuro.uni-jena.de/cat12/) and SPM12 v.6685 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm), running on MATLAB R2015a (Mathworks, Natick, MA, USA). All preprocessing steps are illustrated in Fig. A.2 in the Appendix. The CAT12 processing pipeline was based on recommendations for standardized VBM-based asymmetry analyses (Kurth et al., 2015), accounting for voxel-wise hemispheric correspondence. The pipeline was adapted for longitudinal data by first registering the longitudinal scans, as stated below.

Prior to preprocessing, all raw images were visually inspected for potential artifacts. For each participant, the scans from all four time points were then registered and bias-corrected using the serial longitudinal registration in SPM12, which combines diffeomorphic and rigid-body registration and incorporates a correction for intensity inhomogeneity artifacts (Ashburner and Ridgway, 2012). Specifically, each time-point is a reoriented, spatially warped and intensity biased-corrected version of the average T1-weighted scan, instead of the baseline image, thus avoiding potential asymmetry biases. Thus, the output consisted of an average T1 image and four Jacobian difference maps, representing a measure of voxel compression (values < 1) and expansion (values > 1) necessary for matching each visit scan to the average image. To compute the rate of change over time, a within-subject linear model was used to regress each Jacobian map against time (in years). The resulting beta estimates (hereafter: voxel compression maps; VCMs) were used for later quantification of net grey matter (GM) change.

Each participant's average image was segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) using the CAT12 toolbox with symmetric tissue probability maps (TPMs), computed by flipping and averaging. Spatial normalization was achieved by applying the high-dimensional DARTEL approach (Ashburner, 2007), using a customized study-specific symmetric template, which was created from the original and flipped GM and WM segments of the average T1 image, as described elsewhere (Kurth et al., 2015). Flow fields were created following DARTEL normalization for later transformations into MNI space. Net GM change was quantified by multiplying, voxel-by-voxel, the GM segments with the VCMs (both in native space) and the resulting product images were normalized into MNI space.

2.5. Asymmetry index calculation

To quantify asymmetries in GM volume at baseline and change over time, separate asymmetry indices (AI) were computed based on the average GM segments and the GM change maps, respectively, following procedures described elsewhere (Kurth et al., 2015). Briefly, normalized average segments and change maps were flipped at midline and the resulting images were used to calculate the relative right-left difference in brain size for each participant based on the following formula: (Original − Flipped) / 0.5 × (Original + Flipped). Here, positive AI values indicated rightward brain asymmetries, while negative – leftward asymmetries. A right-hemispheric mask was used to discard the left hemisphere due to redundant information present in both hemispheres[1] and in order to avoid blurring across the midline during spatial smoothing. Finally, the AI maps were smoothed with a kernel of 8-mm full width at half maximum (FWHM) and the resulting images were used for further statistical analyses.

2.6. Statistical analysis

Whole-brain statistical analyses were performed in SPM12 using the spatially normalized and smoothed GM maps to assess whole-brain effects and the corresponding AI maps to analyze brain asymmetries. Second-level general linear models were specified including the following three groups: HC, preHD, and mHD, as well as age, gender, and site as covariates of no interest. Since AI denotes the relative right-left difference in brain size and is not influenced by scaling effects, total intracranial volume (TIV) was only added as a covariate in the baseline whole-brain VBM model. Statistical significance was defined at $p < 0.05$ after cluster-level family-wise error correction (cFWE) for all models. To assess whether whole-brain GM asymmetries were associated with decline in cognitive and motor performance, regression analyses were performed in SPM12 using the AI maps of all HD mutation gene-carriers and the adjusted net 36-month change in scores as a covariate. Separate models were defined for each of the following four scores that have been shown to have the highest rates of decline at 36 months: SDMT, indirect circle tracing, speeded tapping, and grip force variability (Tabrizi et al., 2013).

3. Results

3.1. Whole-brain VBM results

The average GM volumes from the longitudinal registration step and

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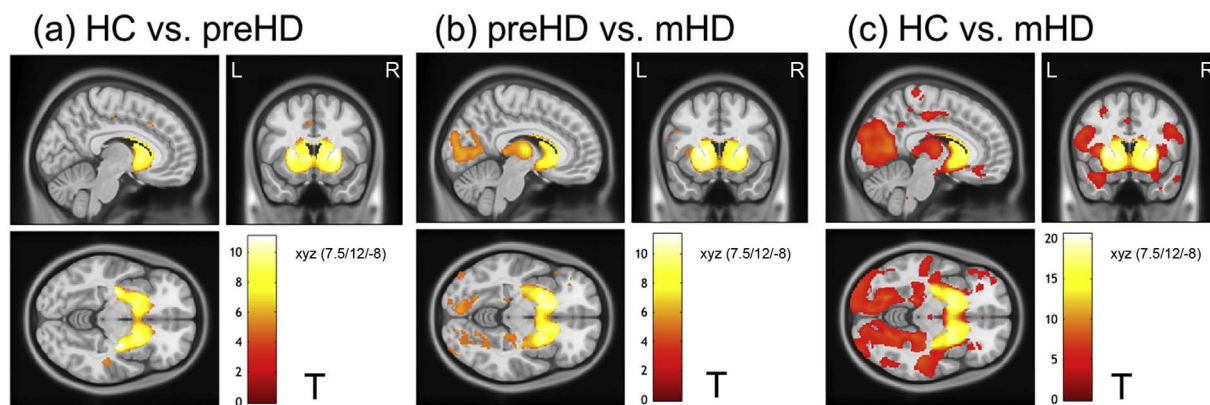[1] Each hemisphere has the same asymmetry index values, but with a different sign.

Fig. 1. Cross-sectional VBM between-group results: (a) healthy controls vs. pre-manifest HD; (b) pre-manifest HD vs. manifest HD; (c) controls vs. manifest HD. Results are significant at p < 0.05 cFWE. MNI coordinates: x = 7.5, y = 12, z = − 8. L = left; R = right.
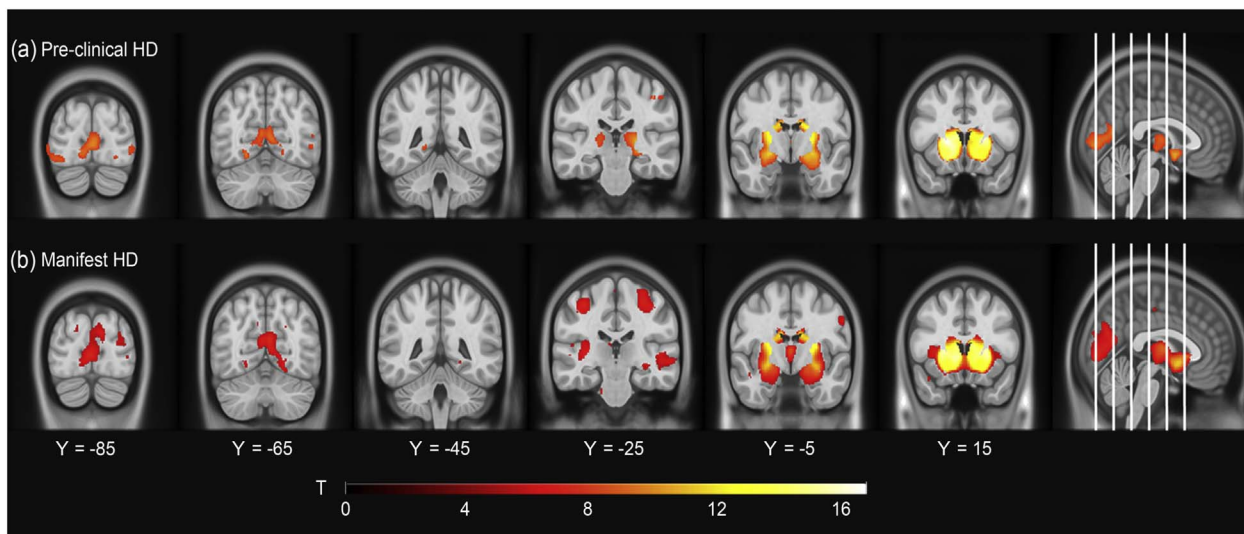

Fig. 2. Longitudinal change in GM volume over 36 months in (a) pre-manifest HD and (b) manifest HD, relative to controls (p < 0.05 cFWE). Results were adjusted for age, sex, study site, and scan interval.

the percent annual GM change (the GM ∗ VCM product divided by 100) were used to assess whole-brain volumetric differences within and between groups. The cross-sectional VBM analysis confirmed the numerous previous reports of localized bilateral striatal loss in preHD relative to controls, while a more widespread bilateral neurodegeneration at the manifest stage was observed, including the occipital, frontal, temporal, and parietal regions (Fig. 1). Longitudinally, GM decline was observed bilaterally in the striatum and the occipital lobe in preHD, as well as in the temporal and parietal regions in mHD (Fig. 2).

3.2. GM asymmetry results

The cross-sectional asymmetry analysis showed left-biased

lateralization of GM loss in the putamen, but only in mHD compared to controls (Fig. 3). Longitudinally, neither within- nor between-group differences were found in GM asymmetries.

3.3. Regression results

In HD mutation gene-carriers, GM volume at baseline was not predictive of net 36-month decline in indirect circle and Q-Motor grip force variability (manumotography) tasks. However, we found associations between GM volume at baseline and future cognitive (SDMT) and Q-Motor finger tapping (digitomotography) decline. This included a positive correlation between decline in SDMT and lower GM volume in the right inferior occipital cortex, right
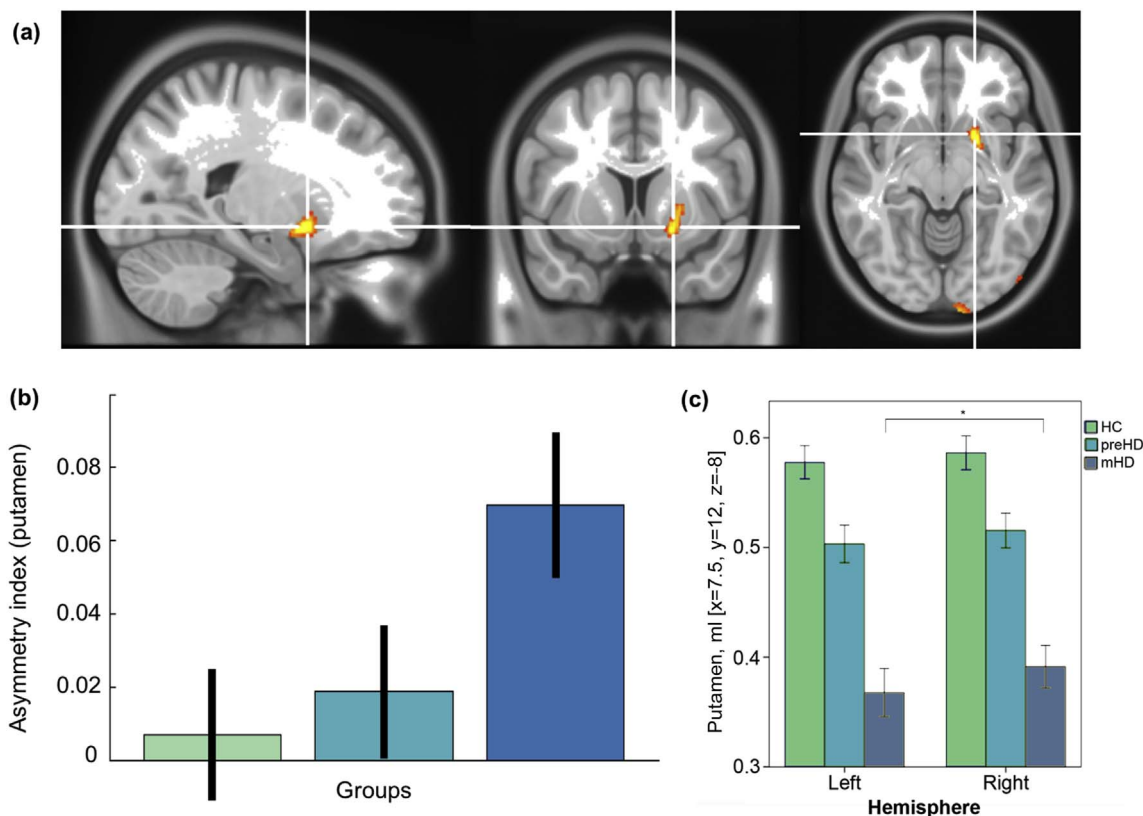
Fig. 3. Cross-sectional VBM-based asymmetry results: (a) voxel-wise group differences (F-test) in GM asymmetries at $p < 0.05$ cFWE; (b) cluster-specific mean asymmetry index (AI) among groups; (c) cluster-specific GM volumes for both hemispheres. Left putamen (in ml) was slightly smaller than the right one ($p = 0.048$).

transverse temporal gyrus, left thalamus, and the precuneus. Additionally, an association was found between decline in Q-Motor finger tapping and lower GM volume in the supplementary motor area and the precuneus (Fig. A.1 and Table A.1 in the Appendix). Similarly, cognitive and motor decline was associated with net 36-month change in GM volume in widespread fronto-striatal and occipital regions, including also the precuneus. In terms of GM asymmetries, no association was found at baseline, but longitudinally, decline in Q-Motor finger tapping was linked to increasing asymmetries of the superior parietal cortex, characterized by more pronounced GM loss in the left than in the right hemisphere (Fig. 4). This result was significant at $p < 0.05$ cFWE-corrected and after Bonferroni correction for the number of performed tests (n = 4).

4. Discussion

In this study, we investigated left-hemisphere vulnerability to neurodegeneration in HD. In particular, our aim was to elucidate whether patterns of asymmetric neuronal loss changed both according to disease stage, and over time, in HD mutation gene-carriers. The cross-sectional asymmetry analysis revealed a significant left-sided lateralization of striatal atrophy in the manifest HD stage, but not in preHD, which is consistent with our initial hypothesis and with previous data (Mühlau et al., 2007). Longitudinally, only bilateral GM loss was found across the HD spectrum, with no evidence for a net 36-month change in GM lateralization. In a regression analysis, we investigated whether asymmetry in GM loss in HD mutation gene-carriers was related to decline in cognitive and motor performance and found that lateralization of GM loss in parietal regions was associated with decline in motor performance when measured with sensitive, Q-Motor tests.

The left-sided lateralization of striatal atrophy found at baseline adds to the growing evidence that the left hemisphere might be more vulnerable to neurodegeneration, especially when individuals are close to disease onset and their overall cognitive and motor abilities have already started to deteriorate. For instance, deficits in visuomotor integration, as measured by the indirect circle tracing task, have been shown to be positively correlated with atrophy of the left somatosensory cortex (Say et al., 2011). Similarly, another study reported worse visuo-motor and visual object performance linked to occipito-temporal atrophy and decreased activity in the left fusiform cortex, in conjunction with increased activity in the left cerebellum (Wolf et al., 2014a). Of note, the latter finding of cerebellar over-
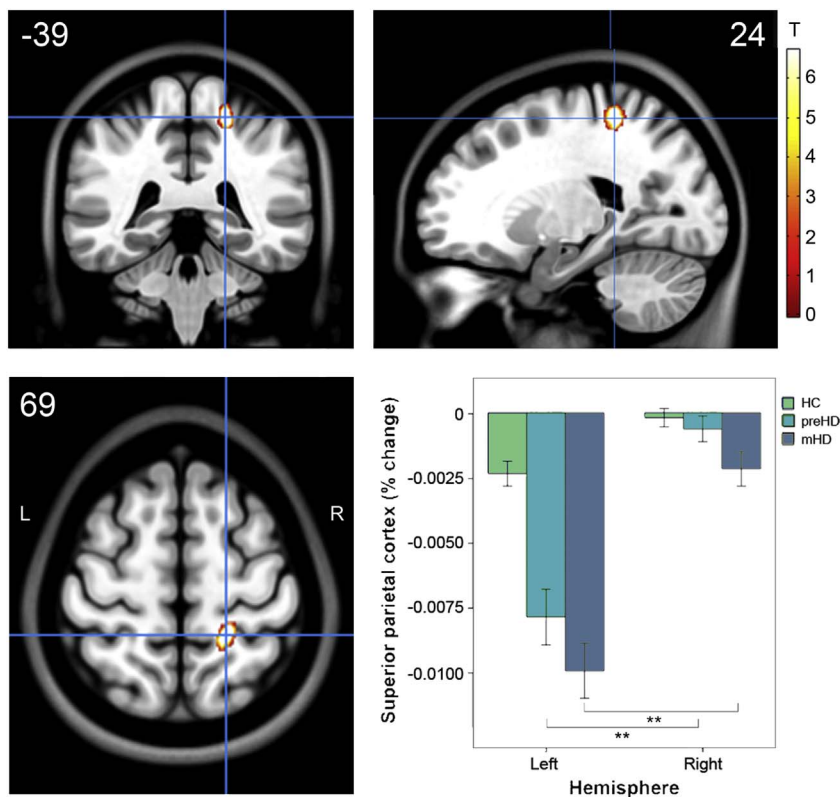
Fig. 4. Association between motor decline and change in GM asymmetries. Net 36-month decline in Q-Motor finger tapping variability [digitomotography] was associated with change in GM asymmetries in the superior parietal cortex with stronger GM loss in the left hemisphere [x = 24, y = − 39, z = 69] (t = 6.07, p = 0.006 cFWE).

recruitment might indicate a disease-specific effect, i.e., a direct consequence of the disease rather than a compensatory change, as recently discussed elsewhere (Cox et al., 2015). In the working memory domain, lower functional connectivity strengths were found between the right putamen and the left superior frontal cortex during a working-memory task in preHD close to clinical onset (Wolf et al., 2008). Finally, in our recent analysis explicitly investigating compensation (Klöppel et al., 2015), we provided further evidence for a higher left-hemispheric susceptibility to effects of regional atrophy, linked to deficits in the motor domain. In contrast, we found indicators for a potential compensatory role of right parietal and frontal areas, in relation to cognitive performance (Klöppel et al., 2015).

A possible explanation is that asymmetries in GM loss are stage-specific and become more pronounced in preHD after some time. Surprisingly, our longitudinal asymmetry analyses did not show any net 36-month change in lateralization of GM loss, neither in preHD nor in mHD. Instead, longitudinal whole-brain group comparisons indicated bilateral progressive GM loss in both HD mutation gene-carriers, especially in the occipital cortex and the precuneus, which is congruous with the increased parieto-occipital disease-specific vulnerability suggested in a recent study and linked to visuo-spatial deficits in HD (Labuschagne et al., 2016).

The lack of longitudinal asymmetry patterns in HD raised the question of whether structural data alone are sensitive enough to detect asymmetric disease progression over a short period of time. Furthermore, HD group stratification was based on disease burden score (DBS) and at the presence of clinical motor symptoms as assessed by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) (Tabrizi et al., 2009), which might have failed to capture the high heterogeneity of the whole HD spectrum. Since previous reports of asymmetric GM loss have been linked to behavioral deficits, we conducted a regression analysis with all HD mutation gene-carriers, including decline in pre-selected cognitive and sensitive Q-Motor assessments as covariates. These included markers of cognitive performance (SDMT and indirect circle tracing test) and Q-Motor measures (finger tapping, [digitomotography] (Bechtel et al., 2010), tongue force variability [glossomotography] (Reilmann et al., 2010b), and grip force variability [manumotography] (Reilmann et al., 2010a), which have previously been reported to have the greatest 36-month decline in HD (Tabrizi et al., 2013). In clinical trial settings, Q-Motor measures exhibited more sensitive to detect treatment effects in the motor domain than the UHDRS-TMS (Reilmann et al., 2015).

In the present study, 36-month decline in SDMT was found to be correlated with lower GM volume at baseline in temporal and parieto-occipital brain areas that are associated with cognitive and visuo-spatial processing and selective attention, which is consistent with previous data in HD (Johnson et al., 2015; Labuschagne et al., 2016; Nana et al., 2014). Similarly, decline in Q-Motor finger tapping

performance (i.e., higher variability in inter-onset intervals) was linked to lower GM volume at baseline in the supplementary motor area (SMA) and the precuneus – areas involved in motor control and also known to be affected in HD (Feigin et al., 2007; Klöppel et al., 2009; Rosas et al., 2008). There was no association found between GM asymmetries at baseline and decline in cognitive or Q-Motor measures. However, the regression analysis using the longitudinal data showed a positive association between decline in the finger tapping task and increased GM asymmetries of the superior parietal cortex in HD mutation gene-carriers. More specifically, higher levels of finger tapping variability (i.e., deterioration in performance) was linked to more pronounced left parietal GM loss, supporting the hypothesis of stronger disease effects targeting the left hemisphere in those with worse motor performance. This is comparable to our previous study on compensation in preHD, reporting a disease effect in the left hemisphere and a compensatory effect in the right (Klöppel et al., 2015).

There are two main limitations of the present study. First, the asymmetry analysis was based on voxel-based morphometry, which does not take into account the contribution of anatomical properties such as thickness, surface area, and gyrification. To address this issue, surface-based analysis might be used in the future to confirm our results. Recently, a novel technique has been proposed for examining shape asymmetries of neuroanatomical structures (Wachinger et al., 2016). Its application to studying Alzheimer's disease showed that shape rather than sized asymmetries might be more sensitive to disease progression. The second main limitation lies in the voxel-based character of the analysis focusing on GM changes only, lateralization on the network level has not been considered. Recently, evidence has been provided suggesting that brain regions with low structural connectivity in the healthy brain, measured using DTI, showed the greatest increases in resting-state functional connectivity in preHD, potentially indicating a compensatory mechanism of functional connectivity accounting for reduction in anatomical links between brain areas (McColgan et al., 2017). Still, the nature of the enhanced functional connectivity at the pre-manifest stage observed in some studies remains unclear. While it may indicate compensation, it might also support the assumption of excitotoxic processes proceeding neurodegeneration (for a review, see Pievani et al., 2014). Irrespectively, data on structural and functional asymmetries in HD on the network level are still lacking and need further investigation.

Overall, this study showed some evidence for a HD-specific lateralization of regional GM loss in more advanced stages of the disease, which were associated with worsening of motor control functions when assessed with sensitive Q-Motor measures. The inability to identify changes in asymmetries in HD over the 3-year period might have resulted from the high level of heterogeneity in terms of functional and structural changes across the HD spectrum. More specifically, classical analyses, focusing on the average effect across a group, may not be sufficient to identify subtle difference, which may provide valuable insights into the pathomechanisms of the disease. Therefore, our results warrant further assessment of brain lateralization to investigate dynamic changes in functional and structural alterations within and between individuals. Hypothetically, individuals with more pronounced atrophy but intact functional capacities might employ a crucial participant-specific compensatory process.

However, the high within-group variability among HD mutation gene-carriers may indicate that such compensatory mechanisms are available to some but not all individuals. A better understanding of the brain mechanisms underlying hemispheric asymmetries in HD may prove useful for the development of future interventions as well as for studying cognitive reserve and compensation. Most importantly, HD may serve as a model disorder in studying compensation in other neurodegenerative diseases, such as Alzheimer's and Parkinson's, and may reveal important mechanistic insights about how the unaffected brain compensates for effects of aging and neuronal loss.

TRACK-HD investigators

Canada A Coleman, R Dar Santos, J Decolongon, A Sturrock (University of British Columbia, Vancouver). France C Jauffret, D Justo, S Lehericy, C Marelli, K Nigaud, R Valabrègue (ICM and APHP, Pitié-Salpêtrière University Hospital, Paris). Germany B Landwehrmeyer (Ulm University, Ulm). Netherlands S J A van den Bogaard, E M Dumas, J van der Grond, E P 't Hart (Leiden University Medical Centre, Leiden). *UK* N Hobbs, N Lahiri, T Pepple, J Read, M Say (University College London, London); D M Cash (IXICO, London).

Conflict of interest

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Dr. Gregory reports no disclosures. She received funding from the Wellcome Trust.

Dr. Scahill reports no disclosures.

Mr. Abdulkadir reports no disclosures.

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Means $\pm$ SD (ranges) are given if not indicated otherwise. Disease burden score (DBS) = age $\times$ (CAG-35.5) (Penney et al., 1997).

Appendix

Table A.1

Regression analysis results: correlations between decline in cognitive and Q-Motor scores and GM volume at baseline.

	Hemi-sphere	Coordinates [MNI]			T	P (cFWE)
		x	y	z		
Positive correlation with SDMT[a]						
Inferior occipital gyrus	R	52	− 69	10	6.32	< 0.001
Transverse temporal gyrus	R	50	− 8	4	6.24	< 0.001
Precuneus	L	− 3	− 67	25	5.36	< 0.001
Thalamus	L	− 16	− 30	− 3	5.13	0.004
Negative correlation with Q-Motor finger tapping variability[a]						
Supplementary motor area	L	− 3	10	49	5.59	< 0.001
Precuneus	L	− 2	− 69	36	5.05	< 0.001

[a] Lower scores in SDMT as well as higher Q-Motor finger tapping scores are both indicative of deterioration.
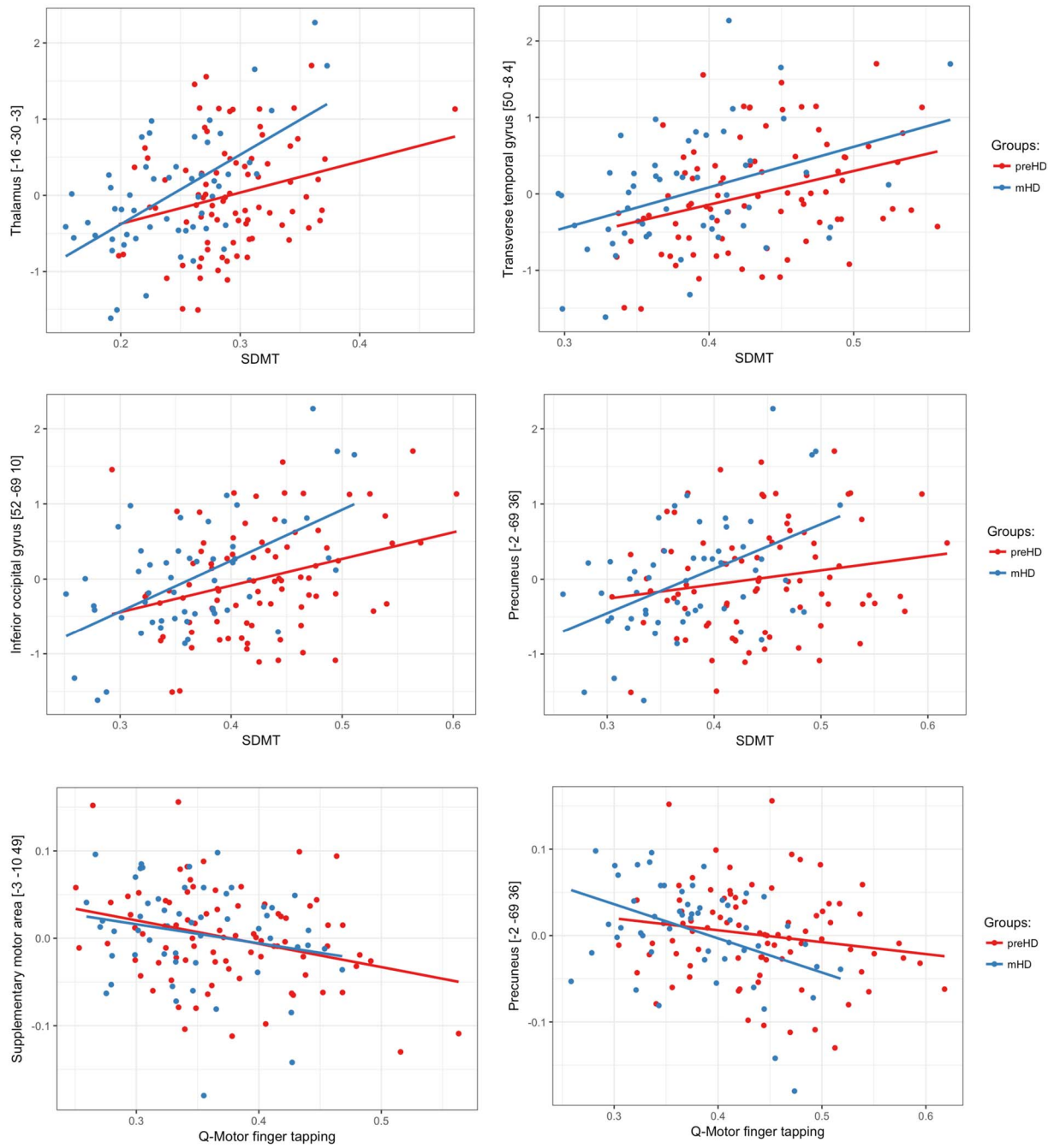
Fig. A.1. Association between decline in behavioral scores and GM volume at baseline (cFWE-corrected). Both lower SDMT scores and higher Q-Motor finger tapping variability [digitomotography] indicate decline in performance.
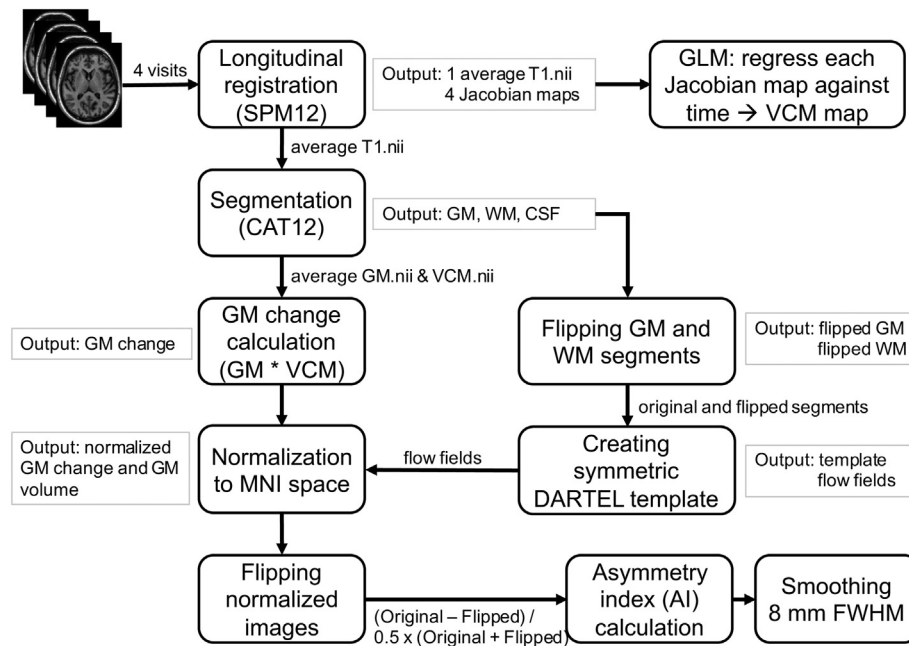
Fig. A.2. Flowchart of the preprocessing pipeline. CSF = cerebrospinal fluid, GM = grey matter volume, VCM = voxel compression map, WM = white matter volume.

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