NeuroImage: Clinical 17 (2018) 312–324

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cross-sectional and longitudinal voxel-based grey matter asymmetries in Huntington's disease

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

ARTICLE INFO

Keywords:
Huntington's disease
Asymmetries
Grey matter volume
MRI
VBM

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.

* Corresponding author at: Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Freiburg Brain Imaging, Breisacher Str. 64, 79106 Freiburg, Germany.
E-mail address: lora.minkova@uniklinik-freiburg.de (L. Minkova).

http://dx.doi.org/10.1016/j.nicl.2017.10.023
Received 6 June 2017; Received in revised form 18 October 2017; Accepted 23 October 2017
Available online 25 October 2017

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

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.