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Extrastriatal degeneration correlates with deficits in the motor domain subscales of the UHDRS

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ABSTRACT

Introduction: Striatal degeneration has significant behavioral effects in patients with Huntington's disease (HD). However, there is scant evidence of the possible contribution of extrastriatal regions to the motor alterations assessed within the different domains of the Unified Huntington's Disease Rating Scale (UHDRS).
Objective: Analyze if extrastriatal grey matter decrease in patients with HD correlates with motor performance assessed with the UHDRS and its different domains.
Method: Twenty-two molecular diagnosed patients with incipient HD, and twenty-two control participants matched for sex and age participated in this study. Voxel-based morphometry (VBM) analyses were done to identify grey matter decrease in the HD patients, and its relationship with the motor deterioration measured with the UHDRS motor scale. To further explore this relationship, a principal component analysis (PCA) was done on the UHDRS domains scores. Then the average of each component was used as a covariate in a VBM analysis. Finally, individual sub-scores from each domain were also tested for correlations with the VBM results.
Results: In addition to the striatal degeneration, the VBM analysis showed significant negative correlations between the global UHDRS scores and the cerebellum, insula and precuneus atrophy. The UHDRS PCA showed component-related negative correlations suggesting a specific impact of individual degenerations. Further analyses with the individual sub-scores showed more specific corelations, including: chorea, with right caudate and left posterior cingulate gyrus; ocular pursuit, with left precentral gyrus, left superior temporal gyrus, cerebellum culmen and right temporal lobe. Saccadic movements with left postcentral gyrus and left middle occipital gyrus.
Conclusion: In the early stages of HD, it is possible to find correlations between behavioral alterations as measured with the UHDRS motor domains, and extrastriatal regions, including specific areas of the cerebellum, and insular, parietal and frontal cortices. These areas could contribute to the HD related impairments along with the classical deficits associated with the striatal degeneration.

1. Introduction

Atrophy in the bilateral striatum in early Huntington's Disease (HD) has been identified using Voxel-based morphometry (VBM) [23]. Neurodegeneration in the caudate, as measured with VBM, in HD has been correlated negatively with motor, cognitive and psychiatric symptoms [5,11,13]. However, the caudate nucleus is not the only structure of the basal ganglia that has been correlated with behavioral measures of HD severity. For instance, globus pallidus and thalamus degeneration have been correlated negatively with scores from the Total Functional Capacity scale (TFC), which measures involve occupation, finances, activities of daily living and care level [5]. Aside from the basal ganglia, other structures have also been implicated in HD, including the possible effect of cerebellar atrophy on motor and

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psychiatric deficits [14].

Clinically, the motor functions in patients with HD are mainly assessed using the Unified Huntington's Disease Rating Scale (UHDRS) [10]. This scale evaluates the performance in a variety of motor domains, including: ocular pursuit movements and saccades, orolingual performance, motor programming, dystonia, chorea and gait. Although the scale has an undisputed clinical value, it is unfortunate that most imaging studies analyzing the possible correlations between motor dysfunction and neuronal degeneration only use the total UHDRS motor score as a covariate. This approach has precluded a better understanding of the possible relationship between different brain areas and scores on specific domains of the UHDRS scale, including the potential contribution of the extrastriatal areas that could be related to specific behaviors measured in each domain of the UHDRS.

Therefore, using the VBM technique, we tested whether motor alterations in the different UHDRS domains are related to decreases over distinct or overlapping brain areas. We evaluated a group of patients with early HD using T1-weighted 3D structural magnetic resonance images (MRI), and compared them with age-matched controls. Then, we analyzed the relationship between brain atrophy and the UHDRS global scores, the results of a principal component analysis (PCA) averaged components, and the UHDRS individual domains from each component.

2. Method

2.1. Participants

Twenty-two patients with HD, confirmed with molecular diagnosis, and twenty-two healthy participants age and sex matched to the HD group, participated in this study (Table 1 for demographics). The healthy volunteers self-reported no history of neurological or psychiatric disorders. All the procedures were performed according to the Declaration of Helsinki [28] and approved by health and ethics committees of the Instituto Nacional de Neurología y Neurocirugía "MVS" and the Universidad Nacional Autónoma de México.

The patients with HD had incipient clinical manifestations according to the scores obtained with the TFC scale and the UHDRS motor scale [10]. After acquiring the UHDRS motor scale, the subscores were fed into a PCA to extract the main components using varimax rotation with a Kaiser normalization.

Table 1
Participant demographics.

	Ctrl	HD
Male:Female	9:13	9:13
Age (years)	45 ± 13	45.6 ± 12.1
CAG repeat length	–	44.3 ± 3.9
Duration of symptoms (years)	–	4.3 ± 3
TFC		11.7 ± 1.8
Disease burden		385.6 ± 100.3
UHDRS motor scale: global score	–	14.6 ± 10.6
UHDRS motor scale: chorea score	–	3.3 ± 3.7
UHDRS motor scale: ocular pursuit score	–	1.4 ± 1.6
UHDRS motor scale: saccadic movements score	–	2.8 ± 2.7
UHDRS motor scale: dysarthria	–	0.4 ± 0.5
UHDRS motor scale: tongue protrusion	–	0.2 ± 0.5
UHDRS motor scale: finger taps	–	1.7 ± 1.1
UHDRS motor scale: pronate/supinate-hands	–	0.6 ± 0.9
UHDRS motor scale: Luria	–	0.6 ± 0.7
UHDRS motor scale: rigidity-arms	–	0.8 ± 0.9
UHDRS motor scale: bradykinesia-body	–	0.6 ± 0.7
UHDRS motor scale: maximal dystonia	–	1.4 ± 2.4
UHDRS motor scale: gait	–	0.5 ± 0.7
UHDRS motor scale: tandem walking	–	0.9 ± 1.1
UHDRS motor scale: retropulsion pull test	–	1 ± 1.5

All the patients with HD were scored according to the components of the UHDRS motor scale, whose range is 0 to 128 and higher scores reflect a greater motor impairment. The highest scores obtained by our patients were in the items: oculomotor pursuit, saccade initiation, saccade velocity, maximal chorea and maximal dystonia. In the Total Functional Capacity Scale (TFC), 11 to 13 scores are defined as the Stage I of the disease. The values represent the mean ± standard deviation.

2.1.1. Image acquisition

All images were acquired using a 3.0 Tesla Achieva MRI scanner (Phillips medical Systems, Eindhoven, The Netherlands) at the Instituto Nacional de Psiquiatría "Ramon de la Fuente Muñiz" in Mexico City. The high-resolution anatomical acquisition consisted of a 3-D_T1 Fast Field-Echo sequence with TR/TE of 8/3.7 ms, FOV of 256 × 256 mm, an acquisition and reconstruction matrix of 256 × 256, resulting in isometric resolution of 1 × 1 × 1 mm.

2.1.2. Voxel-based morphometry

Grey matter volume (GMV) measurements were performed using VBM analysis [1] with FSL (FMRIB Software Library) [21]. First, voxels that did not represent cerebral tissue were excluded through BET software. The resulting images were segmented into grey matter, white matter, and cerebrospinal fluid. The images corresponding to the grey matter from all participants were aligned to Neurological Institute of Montreal MNI152 standard space by means of a nonlinear co-registration. The average of these co-registered images was obtained to generate an HD specific template for this study. In a secondary step, the individual grey matter images were co-registered to this specific template through a non-linear co-registration, and local changes in expansion or contraction were corrected through a process known as modulation [8]. Smoothing was applied with a Gaussian isotropic kernel with a sigma of 3 mm. Using the FSL randomize tool [27] a Two-sample *t*-test was performed between the HD group and controls. Significant degeneration was defined as voxels with a p-value < 0.01.

The associations between grey matter density and the motor deficits in patients with HD were examined using analysis of covariance (ANCOVA). Three different analyses were run. In the first analysis, FSL randomize was fed with the global UHDRS scores. The second analyses used the mean score of each of the resulting UHDRS motor scale PCA components: Component 1, composed by dysarthria, pronate/supinate-hands, maximal dystonia, bradykinesia-body, maximal chorea, finger taps, tongue protrusion and gait; Component 2, composed by rigidity-arms, ocular pursuit and retropulsion test; Component 3, composed by saccade movements and tandem walking; Component 4, Luria. Finally, in the third analysis, scores from the individual domains were tested (Table 1).

All the analyses were corrected using the Threshold-Free Cluster Enhancement analysis (TFCE) with 10,000 randomized permutations [9]. Also, to avoid bias on the multiple comparisons, and as the rotated component matrix showed four independent components, the threshold selected by Bonferroni correction to each domain was 0.01, considering $\alpha = 0.05$. For all the analyses, the disease burden score (calculated using the formula: age × [CAG repeat length − 35.5]) was included as nuisance variable.

Finally, the voxels local maxima *t*-values were used to perform Pearson's correlation analyses between the grey matter density from those regions and the respective behavioral scores, using the Statistical Package for the Social Sciences software (SPSS version 23, Chicago, Illinois, USA). To perform this correlation analysis, the dependent variable was the grey matter density values from each patient, obtained from 4D multi-subject concatenated and smoothed images (GM_mod_merg_s3 file in FSL) and, the independent variable, were the scores obtained by each patient.

3. Results

3.1. HD related grey matter atrophy

The VBM analysis showed a significant GMV decrease in the HD