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Cortical dopamine dysfunction in symptomatic and premanifest Huntington's disease gene carriers

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ABSTRACT

We used ^{11}C-raclopride PET, a marker of D_2 dopamine receptor binding, and statistical parametric mapping (SPM) to localise cortical D_2 receptor dysfunction in individual Huntington's disease (HD) gene carriers (16 symptomatic and 11 premanifest subjects) and assess its clinical significance.
62.5% of symptomatic HD patients and 54.5% of premanifest carriers showed cortical reductions in D_2 binding. The most frequent decreases in cortical binding in individual HD subjects were seen in temporal and frontal areas. Symptomatic HD subjects with decreased cortical D_2 binding had worse scores on neuropsychological tests assessing attention and executive functions than subjects without cortical dopamine dysfunction, notwithstanding comparable reduction in striatal D_2 binding and motor disability. Our results indicate that cortical dopaminergic dysfunction is common in both symptomatic and premanifest HD gene carriers. It is an early event in HD pathophysiology and could contribute to the impairment in neuropsychological performance in these patients.

Introduction

Huntington's disease (HD) is an autosomal, dominant inherited neurodegenerative disorder associated with an expanded number of CAG repeats in the *huntingtin* IT15 gene. The first symptoms are typically choreic movements or neuropsychiatric disorders including depression, psychotic symptoms, and apathy. Cognitive deficits are also common in HD patients and may predate the presentation of motor symptoms by several years (Lemiere et al., 2004; Verny et al., 2007). The spectrum of cognitive dysfunction in HD includes impaired attention, planning and memory, visuospatial capacities, and language (Brandt and Butters, 1996). Many of these cognitive deficits are thought to arise from a fronto-subcortical circuit dysfunction due to the loss of striatal projection neurons, mostly originating from the caudate nucleus (Ho et al., 2003). *In vivo* neuroimaging observations and pathological findings in HD gene carriers also indicate additional involvement of the cortical pathology (Hedreen et al., 1991; Rosas et al., 2003; Zimbelman et al., 2007).

Using ^{11}C-raclopride (RAC) PET and statistical parametric mapping (SPM) to localise significant functional changes at a voxel level, our group has previously detected reductions in D_2 dopamine receptor availability through the whole brain in HD patients (Pavese et al., 2003). Compared to normal controls, the HD patients as a group showed loss of D_2 receptor binding in both striatum and cerebral cortex. In particular, cortical decreases of RAC binding were seen in temporal and frontal areas. However, the role of cortical dysfunctions in the pathophysiology of cognitive disturbances in HD and whether they are an early phenomenon occurring in premanifest carriers is still not clear.

The aims of the current study were to investigate (1) cortical D_2 dopamine receptor availability in individual HD patients and HD premanifest gene carriers and (2) the relationship between loss of cortical and striatal D_2 receptor binding and neuropsychological test scores.

Methods

Subjects

We analyzed RAC PET images of 16 clinically symptomatic HD patients (11 men, age 48.3 ± 6.1 years; mean ± SD) and 11 HD premanifest gene carriers (5 men, age 42.2 ± 7.8 years; mean ± SD) (Table 1). The 16 clinically symptomatic HD patients included the 8 patients who had shown reduced cortical D_2 receptor binding in the SPM between-group comparison with normal subjects in our previous study (Pavese et al., 2003). All subjects had genetically proven CAG repeat expansions of at least 39 in the HD gene. Symptom duration for

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Table 1
Clinical characteristics of symptomatic HD patients, premanifest HD gene carriers, and normal controls.

	Symptomatic HD patients	Premanifest HD gene carriers	Normal controls
No	16	11	13
Sex	11 M/5 F	5 M/6 F	10 M/3 F
Age (mean ± SD) (years)	48.3 ± 6.1	42.2 ± 7.8	50.1 ± 12.0
CAG repeats (mean ± SD)	44.6 ± 3.4	43.2 ± 3.2	–
CAG index* (mean ± SD)	401.4 ± 140.6	303.8 ± 99.3	–
Disease duration (mean ± SD) (years)	5.4 ± 2.8	0	–
UHDRS (mean ± SD)	23.6 ± 13.2	0	–
CTI/953B scanner	9 (7 M/2 F)	0	7 (4 M/3 F)
	Age = 49.3 ± 7.7 years, mean ± SD		Age = 51.3 ± 12.6 years, mean ± SD
CTI/966 scanner	7 (4 M/3 F)	11 (5 M/6 F)	6 (6 M/0 F)
	Age = 46.9 ± 3.3 years, mean ± SD	Age = 42.2 ± 7.8 years, mean ± SD	Age = 48.7 ± 12.4 years, mean ± SD

* CAG index = age × (CAG repeats length − 35.5) (Penney et al., 1997).

affected HD patients ranged from 2 to 16 years with a mean duration of 5.4 ± 2.8 years (mean ± SD). None of the subjects was taking medication known to influence postsynaptic dopaminergic binding at the time of PET and none of the subjects was depressed. Thirteen RAC PET images of normal control subjects from our database were used in SPM comparisons. The mean age of these subjects was 50.1 ± 12 years (mean ± SD) (Table 1).

Clinical and neuropsychological examination

In both premanifest and symptomatic gene carriers, clinical evaluation was performed on the day of PET using the Unified Huntington's Disease Rating Scale (UHDRS) motor assessment score (Huntington Study Group, 1996). Neuropsychological assessment was performed according to the CAPIT-HD (Quinn et al., 1996) within 2 months of PET.

PET scanning

RAC PET was performed with the use of two PET cameras. A CTI/Siemens 953B camera for nine HD patients and seven control subjects. The spatial resolution of this scanner for 31 planes of reconstructed image data in two-dimensional mode is 8.5 × 8.5 mm transaxially and 3.5 mm axially (full-width half-maximum) (Spinks et al., 1992). A 10 min transmission scan was obtained using a retractable external source of $^{68}Ga/^{68}Ge$ to correct for attenuation of gamma-radiation by the brain and skull. A background time frame of 30 seconds preceded the intravenous bolus injection of the ligand. RAC (in 10 ml of normal saline solution) was infused intravenously over 30 seconds. Scanning began at the start of the tracer injection with a protocol of 22 serial time frames collected over 60 minutes. An ECAT EXACT HR++ (CTI/Siemens 966, Knoxville, TN) tomograph with a total axial field of view of 23.4 cm was used for the remaining 7 HD patients, the 11 HD premanifest gene carriers, and 6 control subjects. The camera has a transaxial spatial resolution of 4.8 ± 0.2 mm and axial resolution of 5.6 ± 0.5 mm after image reconstruction (Spinks et al., 2000). A 5-min transmission scan was performed prior to injection of tracer to correct for tissue attenuation of 511 keV gamma-radiation. RAC (in 10 ml of normal saline solution) was infused intravenously over 30 seconds. Scanning began at the start of the tracer injection generating 20 time frames over 65 min.

RAC was supplied by Hammersmith Imanet Ltd.

All subjects were positioned in a way that their orbitomeatal line was parallel to the transaxial plane of the scanner and head position was carefully monitored throughout the scan with the use of laser light applied to face dots.

Data analysis

Parametric images of RAC binding potential (BP) were generated from the dynamic scan series using the BASIS function implementation of the simplified reference region compartmental model with the cerebellum providing the reference tissue input function (Gunn et al., 1997). In addition, an integrated (ADD) image was created by summing the time series of RAC uptake scans collected 0–60 min after tracer administration.

We used SPM (SPM2 software package, Wellcome Department of Cognitive Neuroscience, Institute of Neurology, London, UK, implemented in Matlab5) to interrogate single-subject scans. Each affected HD and premanifest HD gene carrier's PET image was compared statistically to the reference group of healthy control subjects providing a map of statistically different voxel clusters of RAC BP. Because two different scanners were used to study the HD subjects, two reference groups of healthy control subjects scanned with the respective scanners (seven with the CTI/Siemens 953B and six with the CTI/Siemens 966) were employed. Image transformation for interrogation by SPM analysis involved spatially normalizing the PET integrated ADD image to a normal RAC template in Montreal Neurologic Institute (MNI) space created with SPM software and then applying the transformation parameters to the BP image. Parametric images were then spatially smoothed using a 6 × 6 × 6 mm (full-width at half-maximum) isotropic Gaussian kernel. This spatial filter accommodates interindividual anatomic variability and improves signal to noise for the statistical analysis. SPM enables all the parametric images to be transformed into standard stereotaxic space and, consequently, allows comparisons to be made across scan datasets in analogous regions of the brain volume.

SPM comparisons were performed using appropriately weighted contrasts to localize significant decreases in mean voxel BP values. The contrasts were used to derive Z scores on a voxel basis using the general linear model (Friston et al., 1995). Clusters smaller than 50 voxels were excluded. Regional brain differences were considered significant when maps of Z scores exceeded a threshold of 2.33 after correction for cluster size ($p < 0.001$). No global BP normalization was applied. All voxels showing significant RAC BP decreases were also overlaid onto the T1 MRI template image provided by SPM2. All SPMs were viewed by a reader blinded to all patients' clinical information and subsequently divided in two groups: subjects with and without cortical dopamine dysfunction. Neuropsychological test scores, striatal D_2 binding, and UHDRS motor scores were compared between these two groups. Striatal RAC BP values were obtained with a region of interest approach using Analyze software (version 8.0, BRU, Mayo Foundation, Rochester, MN, USA). Parametric images of RAC BP for each subject were anatomically coregistered and resliced to their respective T1-weighted MRI using the Mutual Information Registration algorithm in the SPM2 software package implemented in Matlab5. BP values for the striatum were obtained by defining caudate and putamen region on the individual MR images and applying these regions of interest onto the coregistered parametric images of RAC BP. We calculated putamen (averaged right and left) and caudate (averaged right and left) BPs. The striatal BP was calculated by averaging caudate and putamen results for each patient.