Association Between Motor Symptoms and Brain Metabolism in Early Huntington Disease

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IMPORTANCE Brain hypometabolism is associated with the clinical consequences of the degenerative process, but little is known about regional hypermetabolism, sometimes observed in the brain of patients with clinically manifest Huntington disease (HD). Studying the role of regional hypermetabolism is needed to better understand its interaction with the motor symptoms of the disease.

OBJECTIVE To investigate the association between brain hypometabolism and hypermetabolism with motor scores of patients with early HD.

DESIGN, SETTING, AND PARTICIPANTS This study started in 2001, and analysis was completed in 2016. Sixty symptomatic patients with HD and 15 healthy age-matched control individuals underwent positron emission tomography to measure cerebral metabolism in this cross-sectional study. They also underwent the Unified Huntington’s Disease Rating Scale motor test, and 2 subscores were extracted: (1) a hyperkinetic score, combining dystonia and chorea, and (2) a hypokinetic score, combining bradykinesia and rigidity.

MAIN OUTCOMES AND MEASURES Statistical parametric mapping software (SPM5) was used to identify all hypo- and hypermetabolic regions in patients with HD relative to control individuals. Correlation analyses (P < .001, uncorrected) between motor subscores and brain metabolic values were performed for regions with significant hypometabolism and hypermetabolism.

RESULTS Among 60 patients with HD, 22 were women (36.7%), and the mean (SD) age was 44.6 (7.6) years. Of the 15 control individuals, 7 were women (46.7%), and the mean (SD) age was 42.2 (7.3) years. In statistical parametric mapping, striatal hypometabolism was significantly correlated with the severity of all motor scores. Hypermetabolism was negatively correlated only with hypokinetic scores in the cuneus (z score = 3.95, P < .001), the lingual gyrus (z score = 4.31, P < .001), and the crus I/II of the cerebellum (z score = 3.77, P < .001), a region connected to associative cortical areas. More severe motor scores were associated with higher metabolic values in the inferior parietal lobule, anterior cingulate, inferior temporal lobule, the dentate nucleus, and the cerebellar lobules IV/V, VI, and VIII bilaterally corresponding to the motor regions of the cerebellum (z score = 3.96 and 3.42 in right and left sides, respectively; P < .001).

CONCLUSIONS AND RELEVANCE Striatal hypometabolism is associated with clinical disease severity. Conversely, hypermetabolism is likely compensatory in regions where it is associated with decreasing motor scores. Hypermetabolism might be detrimental in other structures in which it is associated with more severe motor symptoms. In the cerebellum, both compensatory and detrimental contributions seem to occur. This study helps to better understand the motor clinical relevance of hypermetabolic brain regions in HD.

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Motor Symptoms and Brain Metabolism in Early Huntington Disease

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder associated with severe striatal atrophy1,2 and widespread cortical brain changes3 that occur early during the course of the disease.

Fluorodeoxyglucose [18F] ([18F-FDG]) positron emission tomography (PET) has consistently revealed reduced striatal and cortical metabolism in patients with HD that correlates in magnitude with global clinical changes.4-6 Squitieri et al7 demonstrated a linear correlation between the rate of decrease in [18F-FDG] uptake in parietal, occipital, and cingulate cortices and the worsening of the Unified Huntington’s Disease Rating Scale (UHDRS) motor scores in patients with HD. Brain hypometabolism is thus associated with the clinical consequences of the degenerative process. Moreover, the improvement of striatal and cortical hypometabolism may be associated with clinical improvement induced by cell therapy.8

Little is known about regional hypermetabolism sometimes observed in the brain of patients with clinically manifest HD. Focal hypermetabolism has been reported in presymptomatic HD mutation carriers.9-13 However, the detailed pattern and meaning of regional hypermetabolism in patients with HD with clinical symptoms are poorly understood. Three explanations are conceivable: (1) regional hypermetabolism reflects neuronal mechanisms to compensate for the consequences of the disease (ie, involvement of alternative circuits); (2) regional hypermetabolism results from the altered global distribution of cerebral glucose consumption, unrelated to the specific HD clinical status; or (3) regional hypermetabolism reflects local synaptic hyperactivity related to typical HD symptoms (eg, abnormal overflow activation associated with abnormal movements).

We analyzed the distribution of metabolic changes in a cohort of 60 patients at an early stage of the disease to better understand the pathophysiology of regional hypermetabolism in patients with clinically manifest HD. We evaluated the relation of these metabolic changes to hyper- and hypokinetic motor subscores derived from the UHDRS. We identified regions with a probable compensatory role and regions where hypermetabolism presumably reflects synaptic hyperactivity that contributes to motor symptoms.

Methods

Participants

Sixty symptomatic patients with genetically confirmed HD participated in this cross-sectional study. All patients were included either in cell (54 patients) (Multicentric Intracerebral Grafting in Huntington Disease, ClinicalTrials.gov NCT00190450)8,14 or gene (6 patients) therapy programs,8,15 but only baseline evaluations were analyzed here. The mean (SD) age of the patients was 44.6 (7.6) years (range, 28-59 years), and the mean disease duration ranged between 2 months and 16 years (mean [SD], 3.9 [2.8] years). The patients were early in the course of the disease with a mean Total Functional Capacity scale score of higher than 10 at inclusion (mean [SD], 10.7 [1.4]; range, 6-13). The mean (SD) CAG repeat length and Dementia Rating Scale score were 45.2 (7.6) and 129.7 (7.2), respectively. Clinical evaluation was performed using the UHDRS. The Total Motor Score can range from 0 to 124, with higher values indicating greater impairment. Two subscores were extracted: the hyperkinetic score as a combination of dystonia and chorea (sum of items 11 A-E and 12 A-G; range, 0-48) and the hypokinetic score as a combination of bradykinesia and rigidity (sum of items 6 A-B, 7 A-B, 9 A-B, and 10; range, 0-28). The mean (SD) total motor UHDRS score was 35.5 (16.0), ranging from 6 to 87. Hyperkinetic scores ranged from 0 to 48 (mean [SD], 15.4 [8.5]) and hypokinetic scores from 0 to 22 (mean [SD], 8.4 [4.1]).

Fifteen age-matched healthy volunteers8 served as control individuals for the [18F-FDG] PET study (mean [SD] age, 42.2 [7.4] years). They had no history of medical or neurologic illness, had normal brain magnetic resonance imaging, and did not take any medication known to affect FDG uptake.

Ethical permission for this study was obtained from the French National Ethics Committee and the Créteil University Hospital Ethics Committee. Written informed consent was obtained from each patient and volunteer after detailed explanation of the procedures.14 The study was performed in conformity with the Declaration of Helsinki.16

PET Image Acquisition

All PET examinations were performed using a high-resolution EXACT HR+ tomograph (Siemens-CTI), allowing acquisition of 63 simultaneous 2.4-mm-thick axial slices in 3-dimensional mode with an isotropic intrinsic resolution of 4.5 mm on a 128 × 128 voxel matrix. All study participants were placed in a supine position with the head in the middle of the field of view using 3-dimensional laser alignment. A thermoplastic mask molded to each participant’s face minimized head movements. All acquisitions were carried out in a quiet, dark environment while the participants were in a resting state with the eyes closed. To correct for attenuation, a 15-minute transmission scan was performed using germanium 68 rods. Metabolic images were acquired 30 to 50 minutes after a mean (SD) injection of 151 (6.9) MBq of [18F-FDG]. Positron emission tomography emission scans were reconstructed with filtered back
projection with a ramp filter producing images with a resolution of 6.8-mm full-width at half-maximum. Positron emission tomography images were corrected for scatter, γ-ray attenuation, and ¹⁸F decay and then summed from 30 to 50 minutes. All PET images were anonymized and transmitted to the Service Hospitalier Frédéric Joliot site for storage and image processing and analysis.

¹⁸F-FDG PET Image Analysis
Spatial preprocessing and statistical analysis were performed using SPM5 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab 2008 (MathWorks Inc; https://www.mathworks.com). To take into account brain atrophy observed in patients with HD, all PET scans from each patient and control individual were realigned and spatially normalized to an optimized template created using SPM software, mixing control individuals without HD and patients with HD and previously validated. After normalization, all PET scans were smoothed using an 8-mm full-width at half-maximum isotropic gaussian spatial filter to improve the signal-to-noise ratio. The effects of global metabolism were removed by normalizing the count of each voxel to the total count of the brain using proportional scaling. Global normalization was set to 10.

First, we compared the ¹⁸F-FDG scans of the 60 patients with HD and those of the 15 healthy volunteers using an unpaired 2-group t test to detect clusters displaying significant regional differences in ¹⁸F-FDG uptake (Figure 1). The P value (uncorrected) was set at < .001, and only clusters containing more than 20 voxels were deemed to be significant. t Tests were performed with age as covariate.

In each mask, a correlation analysis was performed using a multiple regression model with disease duration as covariate to investigate the association between motor scores and brain metabolism. For the 60 patients with HD, we used an explicit mask to restrict analyses to hypo- or hypermetabolic regions. The statistically significant threshold was fixed at P = .001, uncorrected. Only negative correlations were considered in the regions defined by the hypometabolic mask as they reveal the classic association between low metabolic values and higher motor scores, reflecting more severe disease. The hypermetabolic mask was used to better understand the clinical relevance of hypermetabolic regions: (1) negative correlations associating greater metabolism with a less severe motor score and (2) positive correlations associating greater metabolism with a more severe motor score.

Results
Among 60 patients with HD, 22 were women (36.7%), and of 15 control individuals, 7 were women (46.7%).

Regions With Abnormal Metabolic Values
We observed significant hypometabolism in patients with HD relative to matched control individuals (P < .001; 20 voxels). Analysis using SPM revealed a marked reduction of activity in caudate and putamen nuclei and in multiple cortical areas, such as the frontal and circular regions. Conversely, we found a pattern of hypermetabolism (P < .001; 20 voxels) in the parietal, occipital, thalamus, and several areas in the cerebellum.

Correlation of Motor Scores With Regional Hypometabolism
Only classic association between low ¹⁸F-FDG values and disease severity (higher motor scores) was considered and referred as negative correlation. The extracted regions were therefore related to motor clinical worsening. Hypokinetic motor scores negatively correlated with the metabolic rate (P < .001, uncorrected) in the right caudate body (z score = 4.44) and bilaterally in the middle part of the putamen and pallidum (z score = 3.33 and 3.58 in right and left sides, respectively) (Table 1 and Figure 2A). Hyperkinetic motor scores correlated with the metabolic rate bilaterally in the head and body of the caudate (z score = 5.14 and 5.16 in right and left sides, respectively), in the thalami (z score = 4.43), and in the anterior part of the left putamen (z score = 5.16) (Table 1 and Figure 2B). Other correlations were found in the following cortical regions: bilaterally in the cingulate gyrus (anterior and middle), the parahippocampal gyrus (z score = 3.49 and 3.28 in right and left sides, respectively), the left posterior insula (z score = 4.99), and the right angular area (z score = 4.71; Brodmann area [BA] 40/7) (Figure 2B).

Correlation of Motor Scores With Regional Hypermetabolism
Negative Correlations
Hypokinetic motor scores correlated with hypermetabolic values in the cuneus (z score = 3.70), lingual gyrus (z score = 4.31), and cerebellum (crus I/II, z score = 3.77) (Table 2, Figure 2C, and Figure 3A). We observed no significant negative correlation for hyperkinetic motor scores (Figure 2D).

Positive Correlations
Hypokinetic motor scores correlated with hypermetabolic values in the right inferior parietal lobule, cingulate gyrus (bilaterally, BA 31/32), the right inferior temporal cortex, and the left superior frontal cortex (premotor area) (Table 2 and Figure 2E).
Hyperkinetic motor scores correlated with hypermetabolism bilaterally in the inferior parietal lobule (z score = 4.51), cingulate gyrus (z score = 4.33 and 4.11 in right and left sides, respectively), and left middle frontal gyrus (z score = 4.08) (Table 2 and Figure 2F). In addition, such correlations were found in several regions of the cerebellum, including the vermis, the dentate nuclei, and the cerebellar lobules IV/V, VI, VIII, and IX bilaterally (z score = 3.96 and 3.42 in right and left sides, respectively) (Table 2, Figure 2F, and Figure 3B).

**Discussion**

The main goal of this study was to better understand the association between metabolic abnormalities of the brain and the severity of motor symptoms observed in patients with early symptomatic HD. We observed the main expected correlation between striatal hypometabolism and the degree of motor impairment. We also analyzed the association between hypermetabolic changes in HD brains and motor disorders. We found that some hypermetabolic values correlated negatively with motor scores, such as the cerebellum crus I/II for hypokinetic signs. Conversely, hypermetabolic values positively associated with more severe motor symptoms were found in the inferior parietal lobule; the anterior cingulate; the inferior temporal lobe; and bilaterally in the cerebellar lobules IV/V, VI, VIII, and IX (Figure 2).

We found the striatum of patients with HD to be hypometabolic, as well as several cortical areas, including the cingulate and parietal regions, as previously reported in presymptomatic and symptomatic patients with HD. We confirm the association between hypokinetic motor scores (bradykinesia and rigidity) and striatal hypometabolism. In addition, the correlation between hyperkinetic motor scores and hypometabolism in the anterior part of the left putamen and bilaterally in the caudate nucleus suggests that the anterior part of the striatum may also contribute to hyperkinetic movement disorders.

Striatal hypometabolism is the principal trait of HD, but abnormal hyperactivity has also been reported in several brain regions, such as the cerebellum, the thalamus, and occipital cortex. The pattern of hypermetabolism found in our study is similar to that reported by Feigin and colleagues (Figure 2). Until now, this regional hyperactivity has been considered to be a marker of processes that compensate for the clinical deficits resulting from the disease. Hypermetabolism in these regions would thus be expected to increase when motor scores decrease. Conversely, a positive correlation between metabolism and motor impairment would support the notion that hypermetabolism reflects neuronal hyperactivity detrimental to motor function.

We found such hypermetabolism associated with both increased hypokinetic and hyperkinetic motor symptoms in a consistent subset of regions: the inferior parietal lobule; the anterior cingulate; the inferior temporal lobule; the cerebellar lobules IV/V, VI, VIII, and IX bilaterally; and the dentate nucleus. Hypermetabolism in this subset of regions may be considered to be a marker of the collective motor symptoms of early HD, which fits with several observations in other movement disorders. For example, overactivity of the parietal cortex (BA 40) has been observed in patients with Parkinson disease performing complex manual tasks and has been considered to represent a shift from the deficient striatomesial frontal motor system to the lateral motor system to compensate for bradykinesia. The same region is also hyperactive in DYT1 and DYT6 gene carriers when they exhibit dystonia but not in asymptomatic carriers. These convergent results observed for different movement disorders suggest that the pa...
rietal hypermetabolism observed in patients with HD is unlikely to be a compensatory mechanism but rather detrimental to motor deficit.

Our results suggest that the situation is more complex for the cerebellum. Again, hypermetabolism or hyperactivity in the cerebellum has often been considered to be a compensatory process in patients with movement disorders. Here, we found negative correlations in cerebellar structures connected with associative cortical areas but also positive correlations in motor areas of the cerebellum. Indeed, the severity of both hyperkinetic and hypokinetic motor symptoms was associated with a bilateral increase of metabolism in the dentate nucleus and cerebellar lobules IV, V, VI, VIII, and IX (Figure 3B). These regions belong to the motor structures of the cerebellum and have been found to be overactive in many movement disorders, either hypokinetic (eg, Parkinson disease) or hyperkinetic (eg, tremor, dystonia, and tics). However, previous studies did not investigate the correlation between motor performance or disease severity and cerebellar overactivity. Conversely, our results do not support a consistent compensatory role of hyperactivity in the cerebellum to counteract motor deficits. Both hypokinetic and hyperkinetic clinical manifestations in patients with early HD are associated with hypermetabolism in the same regions.
The hyperactivity of these motor cerebellar regions is more likely to be a marker of the disease itself, reflecting a global disorganization of the neuronal cerebral network involved in motor control. This motor cerebellar hyperactivity is less likely explained by a compensatory process. Indeed, the intensity of this hypermetabolic pattern increases when patients with pre-HD become clinically symptomatic patients.11

We also found that increased metabolism in crus I/II of the cerebellum was associated with less severe hypokinetic symptoms (Figure 3A). Therefore, the hyperactivity in this region is interpreted as an indication of a compensatory process. This region is connected to prefrontal (crus I) and visual (crus II) associative areas and may be integrated in a global system involving visuomotor structures to compensate for hypokinetic movement disturbances.

Higher metabolism is associated with less severe hypokinetic motor scores in the cuneus, the lingual gyrus, and the area of visual integration (BA 18/19). The presence of glucose hypermetabolism in occipital regions is in agreement with the previously mentioned HD-related pattern.34 Hence, Johnson et al35 reported a reduction of cortical thickness in the occipital cortex and lingual gyrus in patients with HD that correlated with visuospatial performance. In addition, Carella et al36 showed that, when movement accuracy is required, patients with HD are more dependent on visual control than individuals without HD or any other abnormalities. Our results also suggest that increased metabolic activity in these regions may participate in compensatory mechanisms for motor disturbances in early HD.

Finally, we did not find any region exhibiting a compensatory effect for hyperkinetic movement disorders. This can be generalized to all hyperkinetic movement disorders: abnormal hyperactivity in brain regions increases with the severity of movement disorders, and the reduction of the movement severity is rather associated with a reduction of this hyperactivity. Therefore, compensation or efficient therapeutic action in these cases is associated with reduced, rather than increased, metabolism.
increased brain activity. This has been shown in tremor, dystonia, and tics. However, because tics can be voluntarily suppressed, reduction of activation in several regions, but also cortical frontal activations, have been associated with the reduction of tics. It remains to be determined whether the compensatory mechanisms in hyperkinetic movement disorders are actually absent or not detectable. For example, the benefits seen from deep brain stimulation in tremor are associated with deep brain stimulation–evoked activations in the same regions that are overactivated by the tremor itself, such as cerebellum and sensorimotor cortex.

Limitations
There were limitations of this study. The correlation analysis performed in this study and shown in Figure 3 cannot rule out a risk of overfitting of the data. We performed an error analysis through a cross-validation by splitting the data obtained in the 60 patients into 50% training and 50% validation subsets with 500 permutations. This did not evidence an overfitting in the present population, although this would need further confirmation in an independent population.

Conclusions
Hypermelabolic changes in early HD are likely associated with both compensatory processes and detrimental effects on motor symptoms. Our hypothesis needs confirmation using longitudinal analysis of metabolic changes during the progression of motor symptoms in patients with HD. Analysis needs to be conducted at the subregional level to infer pathophysiological understanding from associations between metabolism and clinical symptoms in HD. In particular, coexistence of both compensatory and detrimental processes within the cerebellum requires precise anatomofunctional analysis of such abnormalities.

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