Preclinical Huntington's Disease: Compensatory Brain Responses during Learning

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Motor sequence learning is abnormal in presymptomatic Huntington's disease (p-HD). The neural substrates underlying this early manifestation of HD are poorly understood. To study the mechanism of this cognitive abnormality in p-HD, we used positron emission tomography to record brain activity during motor sequence learning in these subjects. Eleven p-HD subjects (age, 45.8 ± 11.0 years; CAG repeat length, 41.6 ± 1.8) and 11 age-matched control subjects (age, 45.3 ± 13.4 years) underwent $H_2{}^{15}O$ positron emission tomography while performing a set of kinematically controlled motor sequence learning and execution tasks. Differences in regional brain activation responses between groups and conditions were assessed. In addition, we identified discrete regions in which learning-related activity correlated with performance. We found that sequence learning was impaired in p-HD subjects despite normal motor performance. In p-HD, activation responses during learning were abnormally increased in the left mediodorsal thalamus and orbitofrontal cortex (OFC; BA 11/47). Impaired learning performance in these subjects was associated with increased activation responses in the precuneus (BA 18/31). These data suggest that enhanced activation of thalamocortical pathways during motor learning can compensate for caudate degeneration in p-HD. Nonetheless, this mechanism may not be sufficient to sustain a normal level of task performance, even during the presymptomatic stage of the disease.

Ann Neurol 2006;59:53–59

A clinical triad of movement, behavioral, and cognitive disorders characterizes Huntington's disease (HD).[1–3] However, the neurodegenerative changes of HD precede the onset of clinical signs and may be associated with subclinical alterations in brain physiology. For example, careful neuropsychological testing can detect abnormalities in presymptomatic carriers of the HD gene mutation (p-HD).[4–7] In this study, we applied functional imaging methods with atrophy correction to elucidate the mechanisms that may underlie preclinical cognitive changes in HD gene carriers.

In earlier imaging studies conducted in the resting state, we used a network approach to demonstrate that HD is associated with an abnormal spatial covariance pattern in both presymptomatic and symptomatic phases of disease.[8,9] This reproducible regional topography is characterized by caudate/putamen and temporal hypometabolism associated with occipital hypermetabolism. Other investigators have found widespread cortical involvement in the early stages of symptomatic HD, in addition to the well-known subcortical features of the disease.[10–12] Given metabolic abnormalities in brain regions subserving both motor and cognitive functions, we now sought to determine whether p-HD subjects acquire sequential information abnormally. We also sought to understand whether p-HD subjects use the same brain regions as control subjects while performing motor learning tasks, and if not, how the early preclinical pathology of HD alters the neural circuitry of learning-related pathways.

Subjects and Methods

Subjects

This study involved two groups of subjects. The first group comprised 11 right-handed p-HD subjects (6 women, 5 men; age, 45.8 ± 11.0 [mean ± standard deviation] years; CAG repeat length, 41.6 ± 1.8; range, 39–45). All subjects had undergone genetic testing before entry into this study

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Received Apr 26, 2005, and in revised form Aug 17. Accepted for publication Aug 17, 2005.

Published online Oct 31, 2005, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20684

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and were known to have CAG repeat expansions. Specific CAG repeat information was available for 10 subjects; 1 subject declined to provide CAG repeat number because of concern regarding confidentiality. These subjects were evaluated by a neurologist (A.F.) experienced with HD and were believed not to have sufficient neurological signs to be diagnosed with HD. Unified Huntington's Disease Rating Scale (UHDRS) scores were as follows: motor, 7.6 ± 9.7; behavioral, 9.5 ± 10.1; independence scale, 100 ± 0; Total Functional Capacity, 12.9 ± 0.3. Neuropsychological testing was normal (eg, Dementia Rating Scale, 139.0 ± 4.2; estimated intelligence quotient, 138.6 ± 31.0; Beck Depression Inventory, 4.1 ± 5.1; Stroop Interference, 47.9 ± 7.7; Symbol-Digit, 58.1 ± 16.9). The second group comprised 11 right-handed age-matched control subjects (6 women, 5 men; age, 45.3 ± 13.4 years). Neurological and neuropsychological testing in these subjects was normal.[13,14]

Tasks

During positron emission tomography (PET) imaging, all subjects performed two reaching tasks with the same kinematic requirements: (1) a motor sequence learning task (SEQ); and (2) a motor execution reference task (CCW). We have used these tasks in previous PET imaging studies of nonmanifesting carriers of genes for hyperkinetic movement disorders.[15] The characteristics of these tasks have been described in detail previously.[16–19] In both tasks, subjects moved a cursor on a digitizing tablet with their right hand out and back from a central starting position to one of eight radial targets displayed on a computer screen. Targets appeared in synchrony with a tone at a 1-second intertone interval in trial blocks of 90 seconds. Target extent was 1cm.

In the CCW reference task, targets appeared in a predictable counterclockwise order, and subjects had to reach the target in synchrony with the tone by initiating the movement before targets appeared.[19–21] Performance was assessed with the following: (1) Timing Error (TE), the difference between the actual time of arrival at the target and the intended time (tone appearance); and (2) Spatial Error, the distance between the center of the target and the point of movement reversal. In the SEQ learning task, the eight targets appeared in a repeating order, and subjects were instructed to learn the sequence while reaching for the targets as they appeared.[17,19,22] At the end of each 90-second trial block, subjects were asked to report the order of the sequence, and a declarative score was computed (range, 0–8; 0 = no awareness of repeating sequence, 8 = complete correct sequence).[16,17,21] For each trial, we also computed a global learning index that reflected explicit learning. In brief, the global learning index was the correct anticipatory movements per trial block.[17–19,22]

In both CCW and SEQ, we computed the means and variances of each performance measure across the entire trial block, as well as for the complete cycle of eight movements. Repeated-measures analysis of variance with post hoc comparisons was performed on each of the analytical variables to assess the effects of groups, cycles, and their interaction.[15,17,21] These analyses were considered significant for p less than 0.05.

We also used published estimates of age of onset probabilities in p-HD to correlate learning performance with years to predicted age of clinical onset.[23] As the predicted age of onset, we selected the age at which gene carriers would be 60% likely (ie, more likely than not) to show signs of HD based on their CAG repeat length and age. We then calculated the difference between this predicted age and the patient's age at the time of our study. This predicted "time to onset" was correlated with the performance variables that differed significantly ($p < 0.05$) between the two groups.

Positron Emission Tomography Scanning

The p-HD and control subjects performed the motor learning (SEQ) and execution (CCW) tasks while undergoing PET imaging. All subjects fasted for a minimum of 6 hours before the imaging experiments. $H_2{}^{15}O$ PET imaging was performed using the GE Advance tomograph at North Shore University Hospital in three-dimensional mode according to procedures described in detail elsewhere.[21,24] During the PET session, each subject was scanned while performing the two tasks in randomized order with the dominant right arm. Each task was repeated twice. For SEQ, different sequences were used for each scan; psychophysical recording of learning performance was acquired for every run. Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject after detailed explanation of the procedures.

Atrophy Correction

We were interested in identifying changes in brain activation responses during the performance of our tasks, without the confound of local anatomical changes associated with striatal volume loss. The latter could potentially correlate with task performance independent of functional changes in regional cerebral blood flow (rCBF) occurring during activation. We therefore performed an atrophy correction on all scans. All subjects underwent anatomical magnetic resonance imaging (MRI) on a 1.5-Tesla GE Signa scanner (GE Medical Systems, Milwaukee, WI) using a spoiled gradient recalled sequence (Timing Error, 5 milliseconds; TR, 24 milliseconds; flip angle, 20 degrees; field of view, 24cm). A computational algorithm was implemented to correct for regional cerebral atrophy, as described previously.[25,26] In brief, the MRI scans were registered to the PET scans and segmented into areas of cerebrospinal fluid and brain tissue. A three-dimensional weighted brain tissue map was created by using image resolution information of the PET scanner. Each PET image was then divided by the weighted brain tissue map on a voxel basis.

Data Analysis

Data processing and analysis were performed using Statistical Parametric Mapping 99 software (SPM99; Wellcome Department of Cognitive Neurology, London, United Kingdom), as described previously.[15] Group comparison of rCBF during motor performance (CCW) was performed by generating SPM{t} maps. To identify voxels that were activated differently in the two groups during learning, we used a two-factor analysis of variance that included both groups (p-HD and control subjects) and conditions (SEQ and CCW). Areas

with increased activation in p-HD subjects relative to control subjects were detected in the model (HD_{SEQ}, HD_{CCW}, $Control_{SEQ}$, $Control_{CCW}$) by specifying a contrast of 1, −1, −1, and 1, respectively; areas with relatively reduced activation in the p-HD group were detected by specifying a contrast of −1, 1, 1, and −1, respectively. In all analyses, activations were considered significant at a threshold of $p = 0.05$, corrected for multiple comparisons at cluster level. To determine whether group differences at the reported voxels were attributed to the reference scans, we performed post hoc comparisons of rCBF within each condition. This was accomplished by drawing 5mm spherical volumes of interest around the voxels with the largest between-group differences and comparing adjusted rCBF values within these volumes of interest across conditions. These effects were considered meaningful for p less than 0.05 (two-tailed Student's t test).

In addition, we performed a separate SPM analysis to correlate regional activity during SEQ with the learning performance measures (global learning index, verbal report). Correlations were considered significant for p less than 0.05, corrected. As described earlier, spherical volumes of interest were centered around the voxels that were found to have the highest correlational significance in the SPM analysis. rCBF measured within these spheres was correlated with each of the two learning indices.

Results

CCW task performance did not differ between p-HD and control subjects. Specifically, when directed to predictable targets, the mean Timing Error for the p-HD group did not differ from that of the control group (p-HD: 36.7 ± 26.1 milliseconds [mean ± standard error of the mean]; control: 16.6 ± 28.6 milliseconds; $p = 0.3$). Spatial Error was also similar for the two groups (p-HD: 0.35 ± 0.06cm; control: 0.31 ± 0.03cm; $p = 0.41$). After atrophy correction, regional activity during the CCW reference task did not differ significantly between the p-HD subjects and the control subjects.

By contrast with the CCW motor execution reference task, learning performance in SEQ was abnormal in p-HD subjects. p-HD carriers learned the sequences more slowly and incompletely (Fig 1A). The mean global learning index was 17.0 ± 5.5 (mean ± standard error of the mean) and 34.9 ± 8.3 ($p < 0.001$), and the verbal report was 3.8 ± 0.6 and 7.8 ± 0.2 ($p < 0.001$) for the p-HD and control groups, respectively. The global learning index correlated with estimates of years to predicted age of onset ($R^2 = 0.52$; $p < 0.02$; see Fig 1B). A similar trend was present for the declarative score ($R^2 = 0.43$; $p = 0.07$).

During SEQ learning, activation was significantly greater in p-HD subjects relative to control subjects (Fig 2) in the left mediodorsal thalamus ($x = -10$; $y = -20$; $z = 10$; $Z_{max} = 4.9$; $p < 0.05$, corrected) and OFC (BA 11/47; $x = -20$; $y = 30$; $z = -22$; $Z_{max} = 4.1$; $p < 0.01$, corrected). In each region, rCBF values for each group and condition are presented in the Table. Post hoc analysis indicated that the group differences in these regions reflected significant increases in SEQ in p-HD ($p < 0.01$) but not in CCW ($p > 0.1$). No areas were activated less in the p-HD group than in the control group.

In addition, p-HD subjects demonstrated a negative correlation between the global learning index and rCBF recorded in the precuneus (BA 18/31; $x = 12$; $y = -69$; $z = 26$; $Z_{max} = 4.57$; $p < 0.001$, corrected;

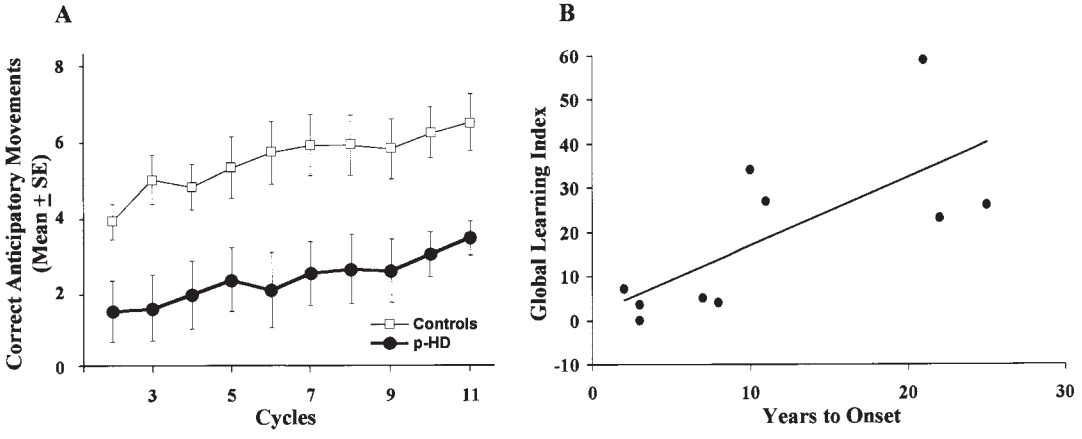

Fig 1. (A) Number of correctly anticipated movements during motor sequence learning in presymptomatic Huntington's disease (p-HD) (filled circles) *and control subjects* (open squares). *Values are plotted as a function of cycles. Anticipatory movements increased over time ($F[1,9] = 9.9$; $p < 0.001$), indicating target prediction and learning.[15,17] However, there was a significant difference between the two groups ($F[1,20] = 9.1$; $p < 0.002$), with diminished learning performance in p-HD. There was no significant interaction between groups and cycles* ($p = 0.6$). *(B) Correlation between sequence learning performance measured by the global learning index and the predicted time (years) to disease onset in p-HD subjects. A significant correlation was present between these two variables* ($R^2 = 0.52$; $p < 0.02$).

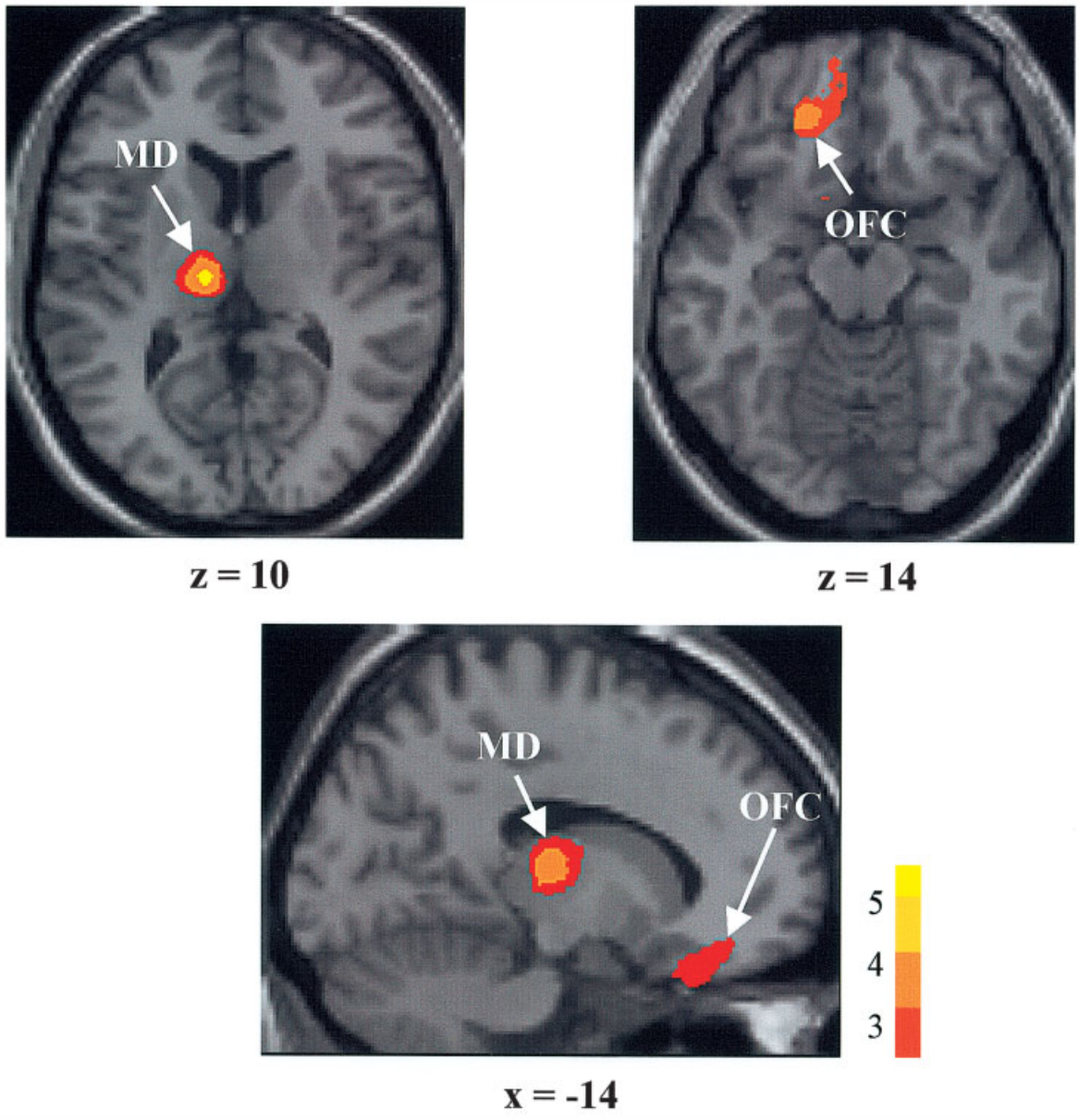

Fig 2. Brain regions in which activation responses recorded during motor sequence learning differed between presymptomatic Huntington's disease (p-HD) and age-matched control subjects (arrows). *Activation in the left mediodorsal thalamus (MD) (left) and orbitofrontal cortex (OFC) (right) was greater in the p-HD group relative to the control group (bottom) (see the Table). The* color stripe *represents* t *values with a threshold at 3.22* ($p < 0.001$).

Fig 3). We also detected a significant positive correlation between the declarative score and rCBF in the head of the caudate nucleus ($R^2 = 0.60$; $p < 0.001$). However, this correlation was not sustained after atrophy correction ($R^2 = 0.12$; $p < 0.1$).

Discussion

Motor sequence learning is abnormal in patients with symptomatic HD[27] and has been reported to be impaired in p-HD subjects as well.[4,28] In this study, we performed PET to measure brain activation during the performance of a motor sequence learning task in p-HD subjects and age-matched control subjects. We sought to identify regional changes that accompany declines in performance in HD gene carriers before the onset of clinical symptoms.

We observed impairment in motor sequence learning in p-HD at a time when motor performance remained relatively preserved. Although there was no statistical difference between the p-HD and control subjects regarding Timing Error, the mean was greater in the p-HD group. This raises the possibility that some of the subjects might have been nearing clinical symptomatology. In fact, based on CAG repeat length

Table. Adjusted rCBF by Condition in Brain Regions That Were Significantly Different between p-HD and Controls

Region	p-HD			Controls			
	SEQ	CCW	Δ[a]	SEQ	CCW	Δ[a]	p[b]
Mediodorsal thalamus	85.4 ± 3.0	83.8 ± 3.3	1.9	83.4 ± 4.0	85.3 ± 3.9	−2.2	<0.0001
Orbitofrontal cortex	68.2 ± 2.6	67.1 ± 3.2	1.6	66.7 ± 5.4	69.0 ± 4.9	−3.2	0.0002

Values represent mean adjusted rCBF (ml/min)/100g ± SD recorded during the performance of a motor SEQ and a CCW (see text).

[a](SEQ − CCW)/CCW × 100%.

[b]Group × task interaction.

rCBF = regional cerebral blood flow; p-HD = presymptomatic Huntington's disease; SEQ = sequence learning task; CCW = motor execution reference task.

and age, several of our subjects were likely to be nearing motor symptom onset. Nonetheless, none could be diagnosed with HD, and it is unlikely that subtle motor problems would have had a significant impact on the learning studies.

Impairment in motor sequence learning in p-HD was accompanied by brain activation responses in the mediodorsal thalamus and the OFC. We have previously found that effective learning performance on our task is normally associated with activation of the dorsolateral prefrontal cortex (DLPFC) and the caudate nucleus.[19,21,22] In HD, however, impaired caudate function may lead to a relative inability to engage the DLPFC for sequence learning. Indeed, although our primary analysis did not detect significantly lower DLPFC activity in the p-HD subjects, this group difference was evident at a liberal hypothesis-testing threshold of $p = 0.05$ (uncorrected). By contrast, our data suggest that to maintain learning performance, p-HD subjects may activate the ventral prefrontal and orbitofrontal regions, perhaps via thalamic projections. Thalamocortical connections that could be relevant to learning are well established, including projections to these cortical zones.[29–31] In agreement with these findings, neuropsychological tests of decision making that use OFC are relatively preserved in early HD,[32] as they were in our presymptomatic subjects.[13,14] Furthermore, caudate pathology in HD progresses from dorsal to ventral,[12,33,34] the dorsal caudate being primarily involved in connections with DLPFC, and the ventral caudate subserving connections to OFC. In p-HD, therefore, both caudate and thalamic activation of OFC may be relatively preserved, allowing this circuit to act in a compensatory fashion for the loss of DLPFC function. Notably, all of the learning-associated activations occurred in the left hemisphere, contralateral to the dominant hand performing the task. Though the analyses involved the subtraction of a

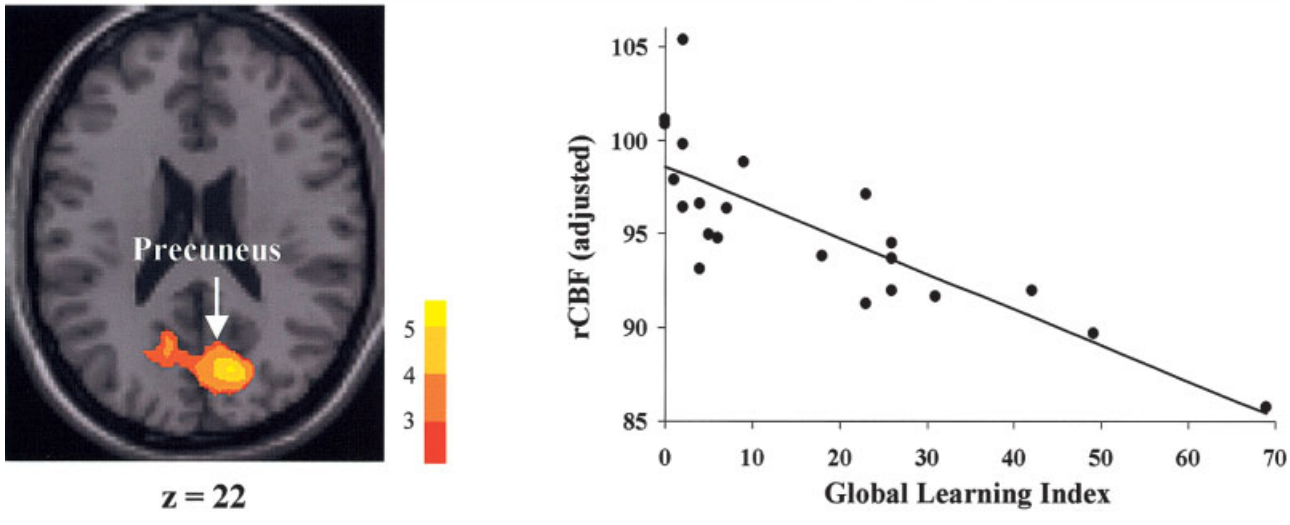

*Fig 3. Results of a Statistical Parametric Mapping (SPM) analysis conducted to detect regions (*arrows*) in which regional cerebral blood flow (rCBF) recorded during motor sequence learning correlated significantly with task performance. In presymptomatic Huntington's disease (p-HD) subjects, rCBF in the precuneus (left) correlated negatively ($R^2 = 0.66$; $p < 0.0001$) with the global learning index (right), suggesting a compensatory mechanism. The* color stripe *represents* t *values with a threshold at 3.55 (*$p < 0.001$*).*

kinematically controlled motor reference task, it is possible that performance of our learning tasks with the nondominant left hand could have produced activation patterns on the other side of the brain.

We also found that a clinical index of learning (global learning) correlated negatively with activity in the precuneus; that is, as learning deteriorates, there is increased activation in this region during task performance. Parietal association regions, including the precuneus, have been implicated in aspects of sequence learning, specifically regarding movement accuracy[35] and retrieval during spatial learning tasks.[36] Furthermore, the mediodorsal thalamus sends projections to the precuneus.[37] Perhaps increased activation in mediodorsal thalamic projections to parietal cortices also acts in a compensatory capacity in our task; that is, the more poorly p-HD subjects perform the task, the more their brains attempt to activate parietal cortices, again with only partial success. Alternatively, this might not be a compensatory reaction, but rather the emergence of an abnormal network that actively interferes with learning. However, this possibility is perhaps less likely given that, as described earlier, thalamic projections to the precuneus are known to be important for both movement accuracy and learning.

Other brain imaging studies have found that p-HD and early HD are characterized by impaired cortical function in regions where there is measurable atrophy, as well as in relatively spared areas. For example, single-photon emission computed tomography perfusion measures in the resting state demonstrate decreased activity in prefrontal cortex, even when atrophy is not present.[38] Similarly, extrastriatal reductions in ^{11}C-raclopride binding also have been observed in HD in amygdala, frontal cortex, and temporal cortex, regions known to be involved with emotional and cognitive function.[39] Perhaps as frontal cortex degenerates, p-HD subjects use relatively preserved parietal cortices to perform motor sequence learning tasks.

Recent brain activation studies in HD are generally in agreement with our findings. For example, during the performance of an "interference" task, p-HD subjects are less able to activate striatocortical pathways to the anterior cingulate.[40] In this functional MRI study, however, the investigators did not identify specific compensatory mechanisms. This difference from our study might have been due to a different activation task and imaging method. In another recent functional MRI study, p-HD subjects were found to have increased frontal activation during the performance of a time discrimination task, despite decreased activation in subcortical structures including the caudate and thalamus.[41] The authors again speculated that some frontal regions were being activated to compensate for the loss of normal striatocortical function. Similarly, in a combined functional MRI and fluorodeoxyglucose PET study of a single HD patient, reduced resting state parietal cortex metabolism was accompanied by abnormally increased local activation during the performance of a visuospatial task.[42] Again, the authors speculated that increased parietal cortex activation was acting to compensate for reduced function in other brain regions. These results and ours suggest that p-HD subjects may be able to compensate during the performance of some tasks at least initially, whereas other tasks may deteriorate more rapidly. Perhaps specific cortical areas involved in the direct pathogenesis of HD preempt the ability of the brain to compensate for some losses of function.

In conclusion, we have found that p-HD subjects activate thalamus and OFC more than age-matched control subjects during the performance of a motor sequence learning task. Even so, p-HD subjects demonstrate impaired learning, with performance correlating directly with caudate activity (without atrophy correction) and indirectly with parietal cortex activity. Taken together, these observations support the idea that the cognitive effects of HD are likely mediated by a combination of striatal dysfunction and the progressive disruption of cognitive circuits involving striatocortical connections.

This research project was funded by the NIH (National Institute of Neurological Disorders and Stroke, RO1 NS 37564, D.E.; R01 NS 40068, J.S.P.; National Institute of Mental Health, R01 MH 01579, J.S.P.); the Huntington's Disease Society of America, the Roy J. and Lucille Carver Trust; and the Howard Hughes Medical Institute.

We thank Dr V. Dhawan and C. Margouleff for their assistance in conducting the PET studies. We offer special thanks to C. Edwards and Dr D. Zgaljardic for their help in subject recruitment and T. Flanagan for manuscript preparation.

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